

Review

Received: 2004.2.8  
 Accepted: 2004.3.05  
 Published:2004.3.10

## Management of Critically Ill Patients with Severe Acute Respiratory Syndrome (SARS)

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Abstract

Severe acute respiratory syndrome (SARS) is frequently complicated with acute respiratory failure. In this article, we aim to focus on the management of the subgroup of SARS patients who are critically ill. Most SARS patients would require high flow oxygen supplementation, 20–30% required intensive care unit (ICU) or high dependency care, and 13–26% developed acute respiratory distress syndrome (ARDS). In some of these patients, the clinical course can progress relentlessly to septic shock and/or multiple organ dysfunction syndrome (MODS). The management of critically ill SARS patients requires timely institution of pharmacotherapy where applicable and supportive treatment (oxygen therapy, noninvasive and invasive ventilation). Superimposed bacterial and other opportunistic infections are common, especially in those treated with mechanical ventilation. Subcutaneous emphysema, pneumothoraces and pneumomediastinum may arise spontaneously or as a result of positive ventilatory assistance. Older age is a consistently a poor prognostic factor. Appropriate use of personal protection equipment and adherence to infection control measures is mandatory for effective infection control. Much of the knowledge about the clinical aspects of SARS is based on retrospective observational data and randomized-controlled trials are required for confirmation. Physicians and scientists all over the world should collaborate to study this condition which may potentially threaten human existence.

Key words

SARS, severe acute respiratory syndrome, critically ill patients, management, treatment and control.

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## 1. Introduction

In 2003, an outbreak of severe acute respiratory syndrome (SARS) caused by the SARS-associated coronavirus involved 26 countries and 8098 patients, resulted in 774 deaths [1]. Thereafter, SARS has re-emerged sporadically in both laboratory and community settings. Its clinical spectrum varies from minimal respiratory symptoms to severe respiratory failure. We have previously contributed to an overview on the contemporary treatment of SARS [2], and the whole topic has also been reviewed elsewhere [3]. In this article, we aim to focus on the management of a subgroup of critically ill SARS patients with more significant respiratory failure.

## 2. Clinico-Radiologico-Pathological Features of Critically Ill SARS Patients

Critically ill SARS patients frequently demonstrate the following clinical features: persistent pyrexia (occasionally from admission but often recurring after an initial period of defervescence), tachycardia (infrequently bradycardia), tachypnoea and significant oxygen desaturation. More than one-third of all the SARS patients required high flow oxygen therapy [4], 20–30% required intensive care unit (ICU) admission or high dependency care, and 13–26% developed acute respiratory distress syndrome (ARDS) [5,6]. The clinical course of some of these patients can progress relentlessly irrespective of all attempts at pharmacological treatment, eventually resulting in septic shock and/or multiple organ dysfunction syndrome (MODS).

Lymphocytopenia, neutrophilia and thrombocytopenia are frequently seen in critically ill SARS patients. Neutrophilia could be due to SARS *per se*, to superimposed infection or related to corticosteroid administration. Pancytopenia, if present, could be due to haemophagocytosis syndrome [7] or reactivation of latent human parvovirus (unpublished data). Prolonged activated partial thromboplastin time and picture of disseminated intravascular coagulation has been reported [8]. Co-infections with other agents including Chlamydia-like agents [9], metapneumovirus [10] or influenza virus (unpublished data) have been reported. Persistent and increasing elevations of creatine kinase, lactate dehydrogenase, and transaminases levels are common [11,12,13]. Associated lung damage is believed to be the result of a virally-triggered inflammatory reaction mediated by a host of cytokines [14,15]. In sicker patients, levels of pro-inflammatory cytokines (IL-1beta, IL-6, IL-8, IL-16, TNF- $\alpha$ ) and TGF- $\beta$ 1 were higher, with slower decline on clinical recovery [14].

Radiographic abnormalities in the chest usually progress upwards from initial unilateral or bilateral lower-to mid-zone peripheral ground-glass shadows, to focal, multifocal or diffuse consolidation. Peak radiographic changes occurred at 8.6 days after fever onset, with 17.4% showing two peaks at 6.3 and 13.5 days, and 4% showing relentless progression [16]. Cavitation is rare but may be associated with superimposed infection in patients with a prolonged illness course and who are mechanically ventilated [17]. High-resolution computer tomography (HRCT) of the thorax showed focal ground-glass and scattered “crazy paving” patterns at presentation, followed by development of interstitial thickening, consolidation, pleural reaction, and scarring and fibrosis in later stages [18,19]. Small (<1 cm) pulmonary cysts may be detected even if the patient is not receiving ventilatory assistance [19]. Subcutaneous emphysema, pneumothoraces or pneumomediastinum are distinct complications of severe SARS [18]. HRCT features of late-stage ARDS caused by SARS are similar to those arising from other causes [19].

Lung biopsy and postmortem studies [20,21] showed acute-phase diffuse alveolar damage (DAD), airspace edema, bronchiolar fibrin, increased numbers of interstitial macrophages (with focal haemophagocytosis) and alveolar macrophages in patients with shorter duration (<10 days) of illness. On the other hand, histology after >10days of illness showed organizing-phase DAD with increased fibrosis, hyperplasia of type II pneumocyte, squamous metaplasia, multinucleated giant cells, and acute bronchopneumonia [20]. In patients who died late in the course of this disease, high loads of viral RNA were detectable by reverse transcriptase polymerase chain reaction (RT-PCR) in the lungs, bowel, lymph nodes, spleen, liver, and kidneys [22].

## 3. Pharmacological Therapy

### General principles

Anti-bacterial therapy for community-acquired pneumonia in accordance with standard guidelines [23] should always be administered before laboratory confirmation of SARS-CoV infection. Where effective anti-viral therapy is available, it should be started as early as possible after diagnosis, and even empirically if suspicious clinical features and especially epidemiological links are present. Since critically ill patients are deemed to have already progressed from the viral replicative phase to the immunopathological phase [5], concomitant institution of an immunomodulatory therapy should also be considered [11]. Since there are no consensus regarding the most optimal treatment regimen in these respects, we will thus review the more commonly used agents and discuss their relative merits based on published reports. When respiratory failure eventually sets in, oxygen supplementation, assisted ventilation and intensive supportive treatments will be required.

#### Antiviral therapy

Ribavirin was the most commonly used empirical antiviral agent for SARS. It is a broad-spectrum purine nucleoside analogue which inhibits both RNA and DNA viruses by interfering with nucleic acid synthesis. There is experimental evidence to show that it has immunomodulatory effects in the treatment of mouse coronavirus hepatitis [24]. Subsequently, it was found that ribavirin has no direct *in vitro* activity against SARS-CoV [25]. Higher doses given intravenously resulted in more frequent and severe adverse effects including haemolytic anaemia, elevated transaminase levels and bradycardia [13].

Lopinavir-ritonavir co-formulation (Kaletra<sup>®</sup>, Abbott Laboratories, USA) is a protease inhibitor for the treatment of human immunodeficiency virus (HIV) infection. It can inhibit the coronaviral proteases, thus blocking the processing of viral replicase polyprotein and preventing the replication of viral RNA. Ritonavir inhibits lopinavir metabolism thus increasing its serum concentration, but it has no activity against SARS-CoV. In a retrospective analysis in Hong Kong [26], 31 patients who had received Kaletra as rescue therapy together with high dose corticosteroids had no difference in rates of oxygen desaturation, intubation and mortality compared with a matched cohort. However, when given as initial treatment in combination with ribavirin in another subgroup of 44 patients, there were significant reductions in the need for rescue pulsed corticosteroid therapy, intubation rate and overall mortality. In addition to the prevalence of diarrhoea among these patients which may render oral drugs more appropriate and useful, synergism between kaletra and ribavirin might have contributed to the benefits since either drug alone has only weak anti-viral activities. Another Hong Kong study of 41 SARS patients treated with a combination of lopinavir/ritonavir and ribavirin compared with 111 patients (historical controls) treated with ribavirin only showed that adverse clinical outcomes (ARDS or death) were significantly lower in the treatment group than in the historical controls at day 21 after symptom onset. Further randomised placebo controlled trials are required [27].

Interferons are a family of cytokines with important roles in the cellular immune response. Interferon  $\alpha$  has been used for SARS treatment in China and Canada [28,29,30]. In an open-label uncontrolled study [28], nine patients treated with corticosteroids plus interferon alfacon-1 (Infergen<sup>®</sup>, InterMune Inc., USA) showed better oxygen saturation, faster radiographic resolution and lesser need for supplemental oxygen compared to 13 given corticosteroids alone. *In vitro* testing showed that interferon  $\beta$  was more potent than interferon  $\alpha$  or  $\gamma$ , being effective even when administered after SARS-CoV infection in cell culture [31].

Traditional Chinese herbal medicine has been used concomitantly with other drugs to treat SARS in mainland China with good results reported [32]. However, its value in critically ill patients has not been reported. Glycyrrhizin, an active component derived from liquorice roots, is effective against SARS-CoV *in vitro* [25]. Its clinical utility remains uncertain. Another herbal compound, Baicalin, also demonstrates anti-SARS-CoV activity *in vitro* (unpublished data).

#### Immunomodulatory therapy

In the absence of an effective antiviral agent in the 2003 outbreak, most physicians had opted to use immunomodulatory agents, most commonly corticosteroids, in the treatment of SARS [11,12,33,34]. It is generally agreed that corticosteroids should not be used during the early viral replicative phase, and that its administration should best coincide with the onset of the immunopathological phase [5]. Clinico-radiological surrogate criteria have been used to indicate the onset of this immune hyperactive phase, thus providing a practical guide to the timing of starting corticosteroids [11]. Corticosteroid dosages

should be high enough, especially in the severe cases, to abort the cytokine storm, and maintained for long enough to prevent the rebound phenomenon [2,29,35]. This may be achieved by using a weight-adjusted [11] and radiographic extent-modified dosages [29] for a period of 2–3 weeks.

In one-third to half of SARS patients, fever may recur while on immunomodulatory treatment due to superimposed infections, too rapid tailing of corticosteroids or persistently severe and uninhibited cytokine storm. Empirical anti-pseudomonal antibiotics should then be given first. If there is no apparent clinical response, opportunistic infections like fungal infection should be excluded. If fever is accompanied by obvious respiratory deterioration in the absence of superimposed pulmonary or systemic infection, most patients can be presumed to be suffering from a severe recrudescence of the SARS illness. In such critically ill SARS patients, further escalation of immunomodulation is warranted. Such deterioration could sometimes occur very rapidly; immediate administration of pulsed methylprednisolone therapy at 500–1000 mg per day intravenously for 2 days, followed by tapering doses in the subsequent weeks, has been associated with improved outcome [11,34]. Up to one-third to one-half of critically ill SARS patients may benefit from this strategy [4,33,34]. Because radiographic abnormalities may lag behind clinical improvement, persistent radiographic shadows *per se*, when accompanied by clinical improvement, do not warrant additional corticosteroids [36].

Human gamma immunoglobulins have been used in selected SARS patients who continued to deteriorate despite treatment [29,33]. An IgM-enriched immunoglobulin product (Pentaglobin<sup>®</sup>, Biotest Pharma GmbH, Germany) has been used in Hong Kong and mainland China [29,35,37]. Pentaglobin at 5mg/kg/day for three days given to 12 patients who deteriorated despite repeated rescue methylprednisolone and ribavirin therapy had shown some improvement in radiographic scores and oxygen requirement [38]. It has been reported that the use of combined methylprednisolone and high-dose intravenous immunoglobulin (0.4g/kg) daily for three consecutive days in 15 probable SARS patients with acute lung injury (ALI) or ARDS had resulted in lower mortality and a trend towards earlier recovery [39]. Randomized controlled trials in larger numbers of patients are required to confirm its efficacy.

Based on the assumption that the neutralizing immunoglobulins in convalescent plasma can curb increases in viral load, convalescent plasma collected from recovered SARS patients has been used in Hong Kong to treat severely ill patients not responding to corticosteroids. Some clinical benefits were reportedly observed in a small number of patients [40].

#### **4. Management of SARS-related respiratory failure**

Despite all efforts, at least 50% of SARS patients would still develop acute hypoxemic respiratory failure, with up to 80% requiring supplemental oxygen [37]. Overall, 20-30% of patients had been admitted into ICU, and 10-20% eventually required intubation and mechanical ventilation [4]. Both non-invasive and invasive ventilatory support has been applied to critically ill SARS patients.

##### Non-invasive ventilation (NIV)

NIV delivers continuous positive airway pressure (CPAP) or bi-level pressure support through a tight-fitting facial or nasal mask. It was commonly employed in many Chinese hospitals [29,31,37,41,42] and our own centre in Hong Kong [11,43,44]. Early application may be beneficial because it could rapidly improve vital signs, oxygenation and tachypnoea [41,43], and may reduce the need for increasing dosages of corticosteroids for progressive respiratory failure. It could avoid intubation and invasive ventilation in up to two-thirds of critically ill SARS patients [29,32,43]. Use of NIV in immunocompromised subjects of other diseases has reported similarly reduced rates of endotracheal intubation and serious complications [45]. NIV in SARS may be of particular benefit, since high dose corticosteroids *per se* would already predispose to ventilator-associated pneumonia, and risks to healthcare workers (HCW) could also be markedly reduced through obviating the need for intubation, a potentially highly infectious procedure. Patients who respond to NIV will usually do so within 24 hours, non-responders who will eventually need endotracheal intubation can thus be identified early [43].

NIV is indicated in the presence of ALI and early ARDS when oxygen saturation (SpO<sub>2</sub>) could not improve to more than 93% despite >5 litres per minute of oxygen; persistent tachypnoea of at least 30 breaths per minute; and progressive radiographic deterioration in the lungs [43]. The usual contraindications to NIV apply, including impaired consciousness, uncooperative patient, high

aspiration risk, and haemodynamic instability [35]. SARS-related respiratory failure responds readily to NIV given at low pressures. CPAP of 4-10 cm H<sub>2</sub>O, or bi-level pressure support with inspiratory positive airway pressure (IPAP) of <10 cm H<sub>2</sub>O and expiratory positive airway pressure (EPAP) of 4-6 cm H<sub>2</sub>O are reasonable starting pressures [43]. Higher pressures should be avoided whenever possible, because it may increase the risk of pneumothorax and pneumomediastinum, which are frequently spontaneous complications of SARS even without assisted positive pressure ventilation [5].

#### Invasive mechanical ventilation

When patients do not improve within one to two days of NIV or continue to deteriorate, or if NIV is contraindicated, endotracheal intubation and mechanical ventilation should be considered. Most centres [64] adopted a ventilatory strategy similar to that recommended for ARDS from other causes [46]. Both pressure and volume control ventilation may be employed [64]. The tidal volume should be kept low (e.g. 5-6 ml/Kg predicted body weight), and plateau pressures maintained below 30 cm H<sub>2</sub>O. Because of a higher risk of barotraumas in SARS, the lowest positive end-expiratory pressure (PEEP) which could achieve satisfactory alveolar recruitment and oxygenation, usually 5-6 cm water, should be employed. Other adjunctive measures employed in the usual ARDS cases had been tried in SARS, including: prone positioning [64,47], high frequency oscillatory ventilation [64,47], nitric oxide [47], high PEEP and regular lung recruitment [64], but their efficacy is uncertain.

Tracheostomy is required in patients requiring prolonged mechanical ventilation and ICU stay. Strict adherence to infection control guidelines is mandatory in performing tracheostomy in the ICU or operating room, as well as during subsequent changes of the tracheostomy tube [48,49].

### **5. Complications**

Critically ill SARS patients on high dose corticosteroids and mechanical ventilation are particularly susceptible to superimposed bacterial and opportunistic infections. Their peripheral blood CD3+, CD4+ and CD8+ were also lower than normal [8,24]. Ventilator-associated infection with organisms like *Pseudomonas aeruginosa*, methicillin-resistant *staphylococcus aureus*, *Acinetobacter baumannii*, as well as invasive mucor sp [50] and aspergillosis [50,51] have been reported. Strict control of hyperglycaemia during corticosteroid administration is essential to reduce the chance of septic complications [52].

Spontaneous subcutaneous emphysema, pneumothoraces and pneumomediastinum are common complications that are potentially aggravated by noninvasive or invasive ventilation [5]. While chest drain insertion is useful to relieve pneumothoraces, prolonged air leak may sometimes occur. By itself, SARS predominantly results in single organ failure of the lungs. Other complications reported are more likely the result of sepsis and its attending problems, including acute renal failure (6%), acute liver failure (1%), rhabdomyolysis, cardiovascular dysfunction, or of prolonged immobilization and underlying co-morbidities, including deep vein thrombosis, pulmonary embolism, ischaemic strokes, etc [53].

### **6. Outcome and prognosis**

The case-fatality ratio (CFR) of SARS has been estimated to range from 0% to >50% depending on the age group affected. The overall CFR is approximately 15% [54]. Variability may be due to different host and viral factors as well as treatment strategies. CFR may also be significantly affected by the duration of follow-up and inclusion of different mixes of suspected, probable and laboratory confirmed cases in different series [55].

Based on the treatment principles presented above, we have developed a standard treatment protocol early on in the outbreak, comprising initially high (but not pulsed) dose methylprednisolone with tapering over three weeks [11]. This protocol was eventually applied to 88 consecutively admitted SARS patients [56]. Their mean age was 42 years, with 97% having laboratory-confirmed SARS. A low overall mortality of 3.4% (3/88) was obtained, with all three deaths occurring in patients over the age of 65 years. Twenty four percent required ICU admission: 14% received NIV (bi-level pressure support) alone and 10% had both NIV and invasive mechanical ventilation. HRCT thorax in all survivors taken 50 days after commencement of treatment showed most did not have clinically significant lung scarring. Another multi-centered study comparing four treatment regimens in Guangzhou, China, also found that a regimen of high dose corticosteroids adjusted according to clinical

and radiological severity, coupled with nasal CPAP ventilation, produced the best result: zero mortality in all 60 clinically-defined SARS patients, mean age 30.5 years. With 40% treated with CPAP and none requiring mechanical ventilation. Subsequently, very low mortality was again recorded among a further 160 patients treated with the same regimen [29].

Many prognostic factors have been reported to independently predict adverse outcome in SARS. They include advanced age [4,57,58,59], diabetes [5,13,59], heart disease [5,59], other significant coexisting conditions [53,59,60], shortness of breath on admission [60], degree of hypoxaemia [58], high total leukocyte count on admission [4,12,60], high initial lactate dehydrogenase [4,57,58], low platelet counts [58], and use of pulsed doses of corticosteroid [4,60]. Compared to patients with nasopharyngeal aspirates negative for SARS-CoV by RT-PCR, PCR-positive ones are more likely to require ICU care and mechanical ventilation, develop acute renal failure and die [60]. In particular, mortality was high among ICU patients: 28-day ICU mortality was variously reported to be 26-37% [42,64,65]. Older age, severity of illness, lymphocyte count, decreased steroid dose, positive fluid balance, chronic disease or immunosuppression, and nosocomial sepsis were associated with poor ICU outcome [65]. Patients who had diarrhoea were more likely to require ventilatory support and ICU care [60]. Higher serum SARS-CoV concentration in the early stage of the disease was a prognostic indicator for later ICU admission [62]. Patients presenting with more extensive radiographic involvement also predicted the need for ICU care or death [63]. Age alone is a consistent and strong prognostic factor in all series. Age-stratified death rates were estimated to be <1% in patients below 24 years of age, 6% between 25 and 44 years, 15% between 45 and 64 years, and >50% in elderly patients over 65 years old [66]. Corresponding estimates in Hong Kong were 13% in those below 60 years of age, and 43% in those over 60 years [67].

The cause of death in SARS is usually progressive respiratory failure with or without concomitant sepsis. Sudden cardiac arrest is also possible, and has been hypothesized to be due to hypoxemia (which would worsen during activities including defaecation), direct viral myocardial injury and extreme anxiety, all of which may lead to electrical instability in the myocardium and induction of arrhythmia [68].

## **7. Infection control measures**

SARS is primarily transmitted by direct or indirect contact of mucous membranes (eyes, nose, or mouth) with infectious respiratory droplets or fomites [12,69]. Transmission risks increase with duration and proximity of contact. Infection control precautions in the ICU are shown in Appendix [70].

Endotracheal intubation should be considered earlier and in anticipation of impending deterioration, so that ample time is available for preparation. It should be performed by the most skilful airway practitioner in a negative-pressure room behind closed doors. Should the operator choose to wear additional personal protective equipment like the Airmate HEPA Powered Air Purifying Respirator System (3M, MN, USA), he/she must be familiar with its mode of operation and the precautions required for gowning and degowning, and must be assisted by a colleague with similar knowledge [11]. A "modified awake" intubation technique has been suggested as the best possible compromise between patient and operator safety by administration of a combination of midazolam, fentanyl and lidocaine until the patient reaches the desired level of sedation [71]. The patient is then paralysed after intubation to minimize coughing. Alternatively, the "rapid sequence induction" technique with intravenous administration of midazolam and suxamethonium can also minimize patient coughing. It should however be emphasized that, unless there is prior preparation for a surgical airway, neuromuscular paralysis should be avoided in anticipated difficult intubation in order to maintain spontaneous respiration [71]. Both bronchoscopy and NIV should be performed in a negative pressure room. Although there is widespread fear of infective risk by NIV [6,55], centres with such experience, including ours, have found that its use is safe if the necessary precautions are taken [11,29,42,43].

Finally, strict adherence to infection control measures in the form of strict isolation and effective cohorting, early diagnosis and contact tracing, timely reporting and institution of public health measures, as well as enhancement of environmental ventilation is key components in the effective management of infectious diseases.

## **8. Conclusion**

Managing critically ill SARS patients is a challenging task. Most, if not all, knowledge about the clinical aspects of SARS are based on retrospective observational data, and randomized-controlled trials are required for confirmation. Physicians and scientists all over the world should collaborate to study this condition which may potentially threaten human existence.

### Conflict of interest

The authors have declared that no conflict of interest exists.

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## **Appendix. Infection control precautions in the ICU**

### *Effective Staff education in Infection Control, emphasizing on*

- Precautions to be used in high-risk procedures and alternative procedures to reduce risks
- Limit opportunities for exposure, e.g., avoid aerosol generating procedures & limit number of health care workers (HCWs) present, alternative nursing practices to limit number of HCWs exposed to each patient
- Effective use of time during patient contact
- “Gowning” and “degowning” without contamination
- Importance of vigilance and adherence to all infection control precautions
- Importance of monitoring their own health
- Dissemination of up-to-date information on SARS and other prevailing infections as they evolve

### *Personal protection equipment (PPE)*

- N95 respirator/surgical mask for airborne/droplet precautions
- N95 mask for high-risk procedures
- Contact precautions: Disposable gloves, gown, cap
- Eye protection with non-reusable goggles and face-shield
- Powered air purification respirators (PAPR) are optional PPE when performing high-risk procedures
- Pens, paper, personal items and medical records should not be allowed into or removed from the patient’s room
- Immediately remove grossly contaminated PPE and shower in nearby facility

### *Environment/Equipment*

- Must conform to U.S. Centers for Disease Control and Prevention recommendations for environmental control of tuberculosis: Minimum 6 air-changes per hour (ACH). Where feasible, increase to  $\geq 12$  ACH + re-circulate air through HEPA filter
- Preferred: Negative pressure isolation rooms with antechambers, with doors closed at all times
- Equipment should not be shared among patients
- Alcohol-based hand and equipment disinfectants should be readily available
- Gloves, gowns, masks and disposal units should be readily available
- Careful and frequent cleaning of surfaces with disposable clothes and alcohol-based detergents
- Use of video camera equipment or windows to monitor patients

### *Patient transport*

- Avoid wherever possible: Balance risks and benefits of investigations which necessitate patient transport

### *Special precautions for ICU*

- A viral/bacterial filter should be placed at the expiratory port of bag-valve mask
- Place two filters per ventilator: Between expiratory port and the ventilator, and another on the exhalation outlet of the ventilator
- Use closed-system in-line suctioning for endotracheal/tracheostomy tubes
- Handle contaminated heat and moisture exchangers (HME) and heated humidifiers carefully
- Scavenger system for exhalation port of ventilator is optional if negative pressure with high air change ( $> 12$ /hour) is achieved
- Preoxygenate patient and temporarily switch off machine whenever ventilator circuit disconnection is required (e.g. For change of ventilator tubings, etc)