SARS in the Intensive Care Unit

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Approximately 20% of patients with severe acute respiratory syndrome (SARS) develop respiratory failure that requires admission to an intensive care unit (ICU). Old age, comorbidity, and elevated lactate dehydrogenase on hospital admission are associated with increased risk for ICU admission. ICU admission usually is late and occurs 8 to 10 days after symptom onset. Acute respiratory distress syndrome occurs in almost all admitted patients and most require mechanical ventilation. ICU admission is associated with significant morbidity, particularly an apparent increase in the incidence of barotrauma and nosocomial sepsis. Long-term mortality for patients admitted to the ICU ranges from 30% to 50%. Many procedures in ICUs pose a high risk for transmission of SARS coronavirus to health care workers. Contact and airborne infection isolation precautions, in addition to standard precautions, should be applied when caring for patients with SARS. Ensuring staff safety is important to maintain staff morale and delivery of adequate services.

Introduction

Severe acute respiratory syndrome (SARS) is a viral pneumonia caused by a novel coronavirus (SARS-CoV) [1]. The SARS epidemic started in November 2002 in the Guangdong province in China and within a few months had affected more than 8000 patients and caused 774 deaths in 26 countries on five continents [2]. Sporadic cases of SARS have been reported recently and highlight the risk for repeated epidemics. A striking feature of SARS during the epidemic was its high rate of nosocomial transmission [2,3] and the high proportion of young, healthy patients who progressed to become critically ill. During the outbreak, approximately 20% to 30% of patients required intensive care unit (ICU) admission [4•,5•,6–9]. Approximately 20% of these admissions were heath care workers [4•,5•]. Therefore, the provision of ICU care plays a potentially important role in the support of patients with severe SARS.

Although considerable progress had been made in understanding the disease [10••], data describing the features, management, and progress of patients with SARS in the ICU are scanty, and published case studies are limited to case studies from Toronto (38 patients) [4•], Singapore (46 patients) [5•], and Hong Kong (54 patients) [11•]. No data exist to allow definitive opinion to be formed on the key issue of best management strategies in the ICU, and this review is limited to providing a synthesis of available descriptive data, consensus opinion, and personal observations.

Intensive Care Unit Admission Criteria and Demographics

The diagnostic and clinical features of SARS have been well-described elsewhere [6,7].

Pneumonia caused by SARS-CoV typically has an insidious onset, and respiratory symptoms worsen slowly but steadily during the first 10 to 15 days [10••]. Published data are consistent and show that the time from symptom onset to ICU admission is approximately 8 to 10 days [4•,5•,11•].

Admission to the ICU is almost always the consequence of progressive, severe respiratory failure, described in currently reported studies as an inability to maintain arterial oxygen saturation more than 90% to 92% despite receiving supplemental oxygen at concentrations of more than 50% to 60% [4•,5•,11•]. On admission, approximately 90% of patients met the clinical criteria of acute respiratory distress syndrome (ARDS; acute onset of bilateral diffuse pulmonary infiltrates on chest radiograph, an arterial oxygen tension to fractional inspired oxygen concentration [PaO_2/FiO_2] ratio of less than 200 mm Hg, and the absence of left atrial hypertension [12]) [4•,5•,11•]. Median Acute Physiology and Chronic Health Evaluation (APACHE) II scores have been reported to range between 11 to 19.5 [4•,5•,11•], and most patients were reported to have isolated respiratory failure on admission [11•].

Several studies have identified prognostic factors for ICU admission or death. These include old age (> 60 years), presence of comorbidities (particularly diabetes mellitus, hepatic or cardiac disease), and elevated lactate dehydrogenase levels on admission to hospital [6,7,13].

Intensive Care Unit Management of SARS

Specific medical therapy

There are some data to suggest that the viral load in the respiratory secretions of patients with SARS is characterized by a peak occurring around the tenth day of illness followed by a decrease in viral load, concomitant with the appearance of an antibody response to the virus [8]. However, in most patients, clinical deterioration occurred progressively during the second week of illness despite a decreasing viral load. This time course supports the suggestion that part of the lung damage may be immunopathologic in nature [7,14•].

This hypothesis provides some theoretical rationale for the use of antiviral agents and immunomodulatory drugs in the treatment of severe SARS. Most patients reported in each of the ICU studies received antiviral agents, predominantly ribavirin [4•,5•,11•]. Ribavirin, a purine nucleoside analogue, has weak antiviral activity and an indirect immunomodulatory effect [15], and was used especially in the early days of the outbreak. Unfortunately, clinical data supporting its clinical efficacy are lacking [16,17]. Other antiviral therapeutic options early in the course of the disease, such as the use of lopinavir/ritonavir in combination, have been tried, but definitive evidence of efficacy is lacking [18].

Immunomodulation with regimens of high-dose methylprednisolone in critically ill patients were used primarily in Hong Kong and in selected cases in Singapore [5•,11•]. Although observational data in SARS suggest high-dose methylprednisolone might be useful in modulating the damage to the lungs [11•,19–22], no good-quality data support its use. The use of steroids for the treatment of other types of ARDS also is controversial. Trials of short-term, high-dose steroid therapy in early ARDS have failed to show a benefit, with some trials showing an increased risk for infection and increased mortality [23]. One study showed that the use of lower doses of steroids in the late phase of ARDS (7–14 days from diagnosis) might favorably modify the fibroproliferative phase of the disease and result in improved oxygenation and successful extubation [24], but the design and interpretation of the trial have proved contentious [25]. High-dose methylprednisolone may potentially cause serious side effects, notably osteonecrosis, which can have significant long-term debilitating effects [10••].

Several other therapeutic options, including intravenous immunoglobulin, immunoglobulin-M–enriched immunoglobulin, and plasma from patients in the convalescent phase, have been used in critically ill patients; however, clinical efficacy is unproven. There is no good evidence to support the use of any specific medical regimen.

Oxygenation and ventilation

Based on the similarity of their clinical [4•,5•,6,7,11•], radiologic [26], and pathologic [14•] features, the severe hypoxemic respiratory failure associated with the SARS-CoV is probably a type of ARDS. Therefore, respiratory support for SARS-induced respiratory failure has generally been similar to that usually used to treat other forms of ARDS.

Failure of simple oxygen supplementation to provide adequate levels of arterial oxygenation and/or the development of respiratory exhaustion results in the requirement for ventilation in approximately 50% to 85% of patients admitted to the ICU [4•,5•,11•]. The results of noninvasive positive pressure ventilation have not been reported, but this mode of ventilation was avoided in our institution (Prince of Wales Hospital) because of risk for infected aerosol generation from mask leakage and high gas-flow compensation [11•].

In view of the obvious similarities to ARDS, patients with SARS in the ICU who require mechanical ventilation have generally been managed with the same ventilation strategy as used previously for patients with ARDS [27•,28]. An approach to minimize ventilator-associated lung injury and improve mortality supports the following: ventilation with low tidal volumes [29•,30], optimizing positive end-expiratory pressure (PEEP) to keep the lungs continuously recruited, minimizing the inspired oxygen concentration to decrease oxygen toxicity, and accepting moderately abnormal physiologic blood gas values when appropriate. Therefore, all ICU studies reported attempts to limit tidal volume to 6 to 8 mL/kg estimated lean body weight, limit the plateau or peak airway pressure to less than 30 to 35 cm H_2O pressure, titrate PEEP to minimize the inspired oxygen concentration, and target moderate arterial oxygen saturation (88% to 95%), while allowing the $PaCO_2$ to increase if necessary, provided the pH was greater than 7.15.

Prone position ventilation is a technique that often improves oxygenation in ARDS [31], possibly through improvements in ventilation perfusion matching, the uniformity of ventilation, and decrease in the compression of the lungs by the heart. Although a recent large, randomized, controlled trial of prone ventilation showed no improvement in mortality or organ dysfunction overall, it might be beneficial in the more severely ill patients [32]. Although prone ventilation was used to a varying degree in mechanically ventilated SARS patients, not enough data are provided to draw any conclusions regarding its efficacy in this setting [4•,5•,11•]. In Hong Kong, the experience with prone ventilation was one of extreme interpatient variability in response (determined by improved oxygenation in the prone position). It is interesting to speculate on the idea that SARS may be a form of ARDS of pulmonary origin (ARDSp), which may have a different pathophysiology than ARDS of extrapulmonary origin (ARDSexp) [33]. In general, ARDSp is associated with more pulmonary consolidation, and ARDSexp with more interstitial edema and compression atelectasis. The latter appears to have a higher potential for alveolar recruitment and clinical response with prone positioning than does the former [34,35]. Whether SARS-induced ARDS falls into the ARDSp category is unknown; however, prone positioning is a relatively safe procedure that rarely worsens a patient's respiratory status. The use of nitric oxide in ARDS had not been shown to improve outcome [36], and anecdotally, the experience in Toronto and Singapore also demonstrates little benefit from nitric oxide in patients with SARS [4•,5•].

Circulatory support and fluid management

In ARDS of non-SARS origin, there is some evidence that restrictive fluid management is associated with better oxygenation, lower mortality, and less patient ventilator days [37,38]. Data from the ICU patients in Hong Kong showed an association between more negative average 24-hour fluid balance and good outcome [11•]. This does not necessarily imply causation, but it may be prudent to restrict fluid intake while maintaining adequate mean arterial pressure and organ perfusion with the appropriate use of diuretics and vasopressors. Hypotension is not a common feature of SARS, and its presence should prompt an active search for possible nosocomial infections.

General management in the intensive care unit

To the authors' knowledge, no significant modifications of general ICU management and organ support other than those dealt with earlier have been reported or recommended.

Intensive Care Unit Outcome

The overall mortality for probable SARS cases reported to the World Health Organization is 9.6% [2]. ICU admission carries a high mortality rate, and for patients admitted to the ICU, the 28-day ICU mortality was 34% in Toronto, 37% in Singapore, and 26% in Hong Kong (with a median APACHE II score of 19.5, 18, and 11, respectively) [4•,5•,11•]. Longer follow-up showed that the ICU mortality increased to 39.4% at 8 weeks in Toronto [4•] and 52.1% at 13 weeks in Singapore [5•]. This is higher than the 180-day mortality rate of 31% reported by the ARDS Network low tidal ventilation trial [29•]. Patients who died were more often older, had higher APACHE II scores, greater comorbidity, and were more likely to have had bilateral radiologic infiltrates on hospital admission [4•,11•]. Terminal events have been reported as severe respiratory failure, sepsis, massive pulmonary embolism, septic shock, and multiple organ failure, or intercurrent medical illness such as acute myocardial infarction [5•].

An unexpected complication observed with alarming frequency in patients with SARS is that of barotrauma-related air leak. The reported incidence of barotrauma (pneumothorax, pneumomediastinum, or subcutaneous emphysema) in the ICU varied between 20% and 30% [4•,5•,11•]. This incidence is high compared with other forms of ARDS [29•]. The risk does not seem to be associated with the use of excessive tidal volume or airway pressure [4•,11•] and is not limited to patients receiving mechanical ventilation [11•]. The exact mechanisms for this observation are unclear, but computed tomography studies in patients with SARS have shown that the diffuse alveolar damage observed in SARS progresses to fibrosis and the formation of cysts [39], and rupture of these cysts could result in extraparenchymal gas leaks.

Nosocomial sepsis is a frequent complication in the ICU. In the Singapore study, 12 of 46 patients (26%) developed positive blood cultures [5•]. In our Hong Kong patients, we observed a high incidence of nosocomial pneumonia (36.5 episodes per 1000 ventilator days) and a high incidence of methicillin-resistant *Staphylococcus aureus* acquisition (25.3% of SARS admissions, Unpublished data). Possible contributing factors include the use of steroids, an increase in the use of prophylactic and pre-emptive antibiotics, and the routine use of gloves and gowns, which have been shown to be associated with poor hand hygiene compliance [40].

Potential long-term complications for ICU survivors include residual pulmonary abnormalities, muscle weakness, post-traumatic stress disorder and depression, and other long-term complications of corticosteroid treatment, such as osteonecrosis [10••]. If steroids have been used in the treatment of SARS, muscle weakness may be an even more prominent feature than might be expected following other causes of ARDS [41].

Infection Control Precautions in the Intensive Care Unit

In addition to the risk from direct patient exposure, many procedures in the ICU pose an additional risk for transmission of SARS-CoV to the health care worker. Because the disease has the ability to produce significant morbidity and incapacitate staff for long periods, staff protection is critical to ensure the provision of adequate ICU services. The US Centers for Disease Control and Prevention has issued guidelines and recommendations on infection control in health care facilities [42•]. We are unaware of any data supporting specific precautions or infection control protocols when caring for patients with SARS in the ICU, and therefore it is considered prudent by some to adopt contact and airborne infection isolation precautions, in addition to standard precautions [42•,43–45]. A brief summary of important aspects of infection control in the ICU follows.

SARS-CoV has been detected in blood, respiratory secretions, feces, urine, and various tissue specimens. Particularly high viral RNA concentrations have been detected in respiratory secretions and feces [46]. Although mechanisms have not yet been fully elucidated, spread probably occurs most often through droplets and aerosols. Spread may be enhanced by the use of nebulizers or similar devices [47]. Cross-infection by fecal matter also has been linked to contaminated sewage systems [48]. The virus is stable on surfaces for days after shedding, and therefore, in ICU environments where patients with SARS may be clustered together, potentially high viral concentrations mandate strict adherence to infection control procedure to prevent transmission.

Patient isolation
Patients should be admitted to a single-patient airborne infection isolation room. These rooms should have at least six to 12 air exchanges per hour [49], monitored negative pressure relative to hallways, and air exhausted directly to the outside or passed through a high-efficiency purifying air filter if recirculated. An antechamber is preferred. Adequate patient-dedicated equipment should be provided, and medical staff should be limited to the number sufficient to meet patient-care needs. If there is a lack of isolation rooms, a cohorting strategy to physically separate the SARS patients may provide some advantage.

Personal protective equipment
Gloves and gowns, respiratory protection, and eye protection should be put on before entering a SARS patient care area. Personal protective equipment should be worn and removed in separate, designated "gown-up" and "gown-down" areas, and this should be done safely to prevent contamination of clothing and skin.

Disposable particulate respirators (*eg*, N95, N99, or N100) are considered sufficient for routine respiratory protection for airborne infection isolation and are the minimum level of respiratory protection required for aerosol-generating procedures. Details on a respiratory protection program can be assessed from the Unites States Occupational Safety and Health Administration [50].

It is prudent to wear eye protection within 3 feet of a patient with SARS. If splash or spray of respiratory secretions or other body fluids is likely, goggles are recommended. Hand hygiene (*ie*, hand-washing or use of an alcohol-based hand rub) should be performed after contact with the patient or his/her environment of care. In the ICU, it is important to reinforce this behavior because excessive gloving and gowning may compromise hand hygiene compliance [40].

Oxygen therapy and mechanical ventilation
The use of entrainment or Venturi-type masks should be carefully considered because the high gas flows generated might encourage dispersal of contaminated droplets. Procedures like bag-valve-mask ventilation, intubation, and suctioning may impose high risk for transmission of SARS-CoV because of air leak, coughing, agitation, and generation of aerosols, and should be minimized by good technique. All staff should wear protective equipment appropriate for droplet, contact, and airborne transmission, which includes a mask at N95 level or higher, goggles, full-face shield, cap, gown, and gloves. In our experience, these precautions provide a good level of protection to staff, although some authors recommended a higher level of contact and respiratory protection [4•,5•], including powered air purification respirators (PAPRs). After the intubation procedure, all wastes and disposable items should be carefully disposed of, and the environment should be cleaned and disinfected. Filters with high-efficiency bacterial and viral filtration properties, and safe scavenging systems should be incorporated into respiratory circuits whenever possible. Open suction should be avoided after intubation, while patients receive mechanical ventilation.

Aerosol-generating procedures
These procedures include nebulization, diagnostic sputum induction, bronchoscopy, open airway suctioning, positive pressure ventilation through face mask, and endotracheal intubation. The level of protection for health care workers who perform these procedures should be maximized as noted earlier depending on available resources. If possible, the procedure should be performed in an isolation area. Other options include surgical hoods, disposable full-body isolation suits, and PAPRs.

Environment
Cleaning and disinfection of environmental surfaces with appropriate solutions such as chloride and hypochlorite are important components of infection control [51]. It is prudent to wipe the external surfaces of all equipment with an Environmental Protection Agency–approved hospital disinfectant upon removal from the patient's room.

Staff Education and Health
Staff should be fully informed regarding relevant advances in knowledge of SARS and properly educated on infection control precautions. A special room distant from the unit is preferred for meals and rest. Routine staff screening, monitoring, and quarantine procedures should be followed. During a SARS outbreak, health care workers are faced with the stresses of working in strict respiratory isolation, caring for their own colleagues with SARS, and worrying about getting the disease themselves or infecting loved ones [4•]. How to deliver intensive care efficiently and compassionately while protecting oneself and others from infection is a great challenge, but ensuring the safety of the staff and providing timely psychological peer support would appear prudent to maintain morale.

Intensive Care Unit Resource Implications During SARS
Critical care resources can be significantly strained during a SARS outbreak, as a result of influx of SARS patients, the closing of institutions for quarantine, and illness or quarantine of health care workers. In the Toronto report, transmission of SARS resulted in closure of 73 medical-surgical ICU beds and the quarantine of 164 ICU health care workers [4•]. Because of this strain on ICU services, each health district should develop contingency plans for increasing its

capacity to treat critically ill patients in respiratory isolation, should the need arise.

Conclusions

No specific treatment regimen can be recommended for treatment of SARS, but ICU supportive care is required for approximately 20% of infected cases. ICU admission is associated with significant morbidity and mortality. For patients requiring mechanical ventilation, a lung-protective strategy using low tidal volumes has been used with reasonable success. Fluid restriction is easy to achieve and may be associated with improved outcome. Many procedures in the ICU are associated with a high risk for transmission of SARS-CoV to health care workers; therefore, strict infection control precautions should be taken. A SARS outbreak could greatly strain regional critical care resources, and staff protection is critical to maintain adequate services.

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