

# Severe Acute Respiratory Syndrome

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## Introduction

Severe acute respiratory syndrome (SARS) is a new clinical entity which was first observed in Guangdong, China at the end of 2002. Since then there have been more than 7000 probable cases worldwide and more than 800 deaths. The difficulties of managing patients with this potentially fatal condition have been compounded by a lack of data relating to the condition and its highly infectious nature. Although the disease appears to have been brought under control, at least temporarily, a resurgence cannot be discounted and it is important that the medical community be prepared for this. This article summarizes current knowledge of SARS, with particular reference to Intensive Care. Where possible the information given is based on published data but there are no data specifically related to Intensive Care management and therefore some information is based on the opinion of the Intensive Care teams at the Prince of Wales Hospital and Tuen Mun Hospital, Hong Kong. It should be noted, however, that this is a rapidly evolving area of knowledge. Regularly updated information is available at <http://www.aic.cuhk.edu.hk/web8>.

## Epidemiology and aetiology

Although both SARS corona virus (SARS-CoV) and a metapneumovirus have been implicated in the causation of SARS, SARS-CoV appears to be the aetiological agent in the vast majority of cases [1-3]. This virus is an enveloped ribonucleic acid virus which is related to viruses known to be major causes of the common cold and viruses that have been reported to

be an important cause of pneumonia in military recruits [3].

The pattern of spread of the disease suggests that transmission is by respiratory droplets and fomites but also possibly via airborne spread and excreta. Although the disease is moderately contagious it appears to be selectively contagious with some very close contacts of patients remaining non-infected [4,5]. A striking feature of the disease is the number of healthcare workers who have been infected, in some cases despite taking precautions to avoid infection [6,7]. Probable cases have occurred in many countries around the world with major outbreaks in China, Taiwan, Hong Kong, Singapore, Toronto and Hanoi. Approximately 20-25% of patients with SARS require admission to Intensive Care [8].

## Pathogenesis

The pathogenesis of the disease is unclear but it is currently believed that the early clinical features may be due to infection with the virus and viral replication with later features being due to the host response to infection [9]. Results from post mortem studies demonstrate diffuse alveolar damage, epithelial cell proliferation and an increase in macrophages in the lung. Haemophagocytosis is present in some patients, supporting the suggestion that the disease is, in part, due to the host response to infection [10].

## Clinical features [8,9,11,12]

The mean incubation period is 6.4 days with a standard deviation of 4.08 days [11].

Common early clinical features include fever, chills, rigors, headache, malaise and myalgia. Mild respiratory symptoms may be present, as may nausea, vomiting and diarrhoea. Note that fever is not always present, particularly in the elderly and up to 10% of patients may be afebrile throughout their ill-

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ness. Later, usually in the second week of the illness, respiratory symptoms become more prominent with the onset of a dry, non-productive cough and dyspnoea. The patient may develop hypoxaemia and inspiratory crackles. Spontaneous pneumomediastinum occurs in about 12% of patients. Approximately 20-25% of patients require ICU admission, of which about a half require mechanical ventilation and approximately 85% develop clinical and radiological features compatible with ARDS. Approximately 20-35% of patients who are mechanically ventilated develop ventilator associated pneumomediastinum or pneumothorax despite a low tidal volume, low inspiratory pressure strategy [13,14]. Diarrhoea is a prominent feature, occurring in a large proportion of patients. It is usually high volume watery diarrhoea without blood or mucus. Haematological involvement is common with lymphopaenia in 98%, neutrophilia in 82%, thrombocytopenia in 55%, thrombocytosis in 49% and isolated prolonged activated partial thromboplastin time in 63%. Lymphopaenia occurs as a result of a fall in T cell counts. D-dimers are often raised but disseminated intravascular coagulation is uncommon [15]. Mild cardiovascular failure is common after instituting mechanical ventilation but otherwise significant other organ failure is unusual [13] and may be a sign of superadded bacterial infection.

The World Health Organization has published surveillance criteria for probable cases (<http://www.who.int/csr/sars/casedefinition/en/>) which emphasize fever and respiratory symptoms but it should be noted that these criteria are designed for epidemiological purposes and not for use as clinical criteria for diagnosing SARS. Data from a surveillance clinic for healthcare workers exposed to patients with SARS indicates that the criteria are specific but insensitive when used for clinical purposes [12].

### **Radiological and biochemical features [8,16]**

Serum concentrations of creatine phosphokinase and hepatic transaminases may be raised and a rise in the serum concentration of lactate dehydrogenase is common. Hyponatraemia and hypokalaemia occur in about 20-25% of patients. The chest X-ray may be normal in up to 20% of patients at presentation and abnormalities are non-specific. Typically focal infiltrates, predominantly affecting peripheral zones

progress to more generalized, patchy, interstitial infiltrates with areas of consolidation occurring in late stages. Pleural effusions, cavitation and hilar lymphadenopathy do not appear to be features of the syndrome. High resolution computerized tomography (HRCT) is more sensitive. Changes include ill defined peripheral ground glass opacities, usually in a subpleural location, traction bronchiectasis and interlobular septal and intralobular interstitial thickening. Examples of radiological changes can be seen at [http://www.droid.cuhk.edu.hk/web/atypical\\_pneumonia/atypical\\_pneumonia.htm](http://www.droid.cuhk.edu.hk/web/atypical_pneumonia/atypical_pneumonia.htm). In patients in the late stage of severe disease requiring ICU admission HRCT shows changes consistent with the late phase of acute respiratory distress syndrome (ARDS).

### **Management**

Infection control is a vital part of management and its importance cannot be overemphasized. A significant proportion of patients in major outbreaks have been healthcare staff [8,17]. As well as the major consequences for the individuals this may have major impact on the ability of the healthcare facility to deal with an outbreak by increasing workload while reducing the staff available to carry out the work and by the negative impact on staff morale [13]. In addition nosocomial infection of patients admitted with other conditions may be a significant problem [8].

Hospital infection control procedures are largely based on experience with other diseases and our limited understanding of the modes of transmission of the disease. It is important that senior members of the Intensive Care team take an active role in infection control, examining all practices in the ICU for potential infection risk and ensuring compliance with infection control. Guidelines on hospital infection control and on home infection control procedures for staff exposed to SARS patients are available from both the WHO (<http://www.who.int/csr/sars/infectioncontrol/en/>) and Centers for Disease Control and Prevention (<http://www.cdc.gov/ncidod/sars/ic.htm>). Details of ICU infection control procedures carried out in the Prince of Wales Hospital, Hong Kong are available at <http://www.aic.cuhk.edu.hk/web8>. In brief, all staff were required to wear an impermeable gown, a fit-tested N95 or N100 mask, full face shield and gloves while working in the ICU. Fit testing of masks is important as any given mask will not adequately fit a substantial pro-

portion of staff. Equipment must be donned and removed in the correct order. Separate areas were provided outside the main entrance of the ICU for donning and removing personal protective equipment. A nurse was allocated to ensure compliance and all staff were encouraged to look after their colleagues by pointing out mistakes. Special precautions were taken for disposing of excreta and vomitus and for potentially high risk procedures such as intubation and extubation. Non-invasive ventilation was not used, in line with the recommendation by the manufacturer of BiPAP machines that BiPAP should only be used for patients with SARS if complete respiratory isolation is possible. Special precautions were taken to minimize the risks to staff associated with invasive mechanical ventilation and manual ventilation with self-inflating resuscitators. All expired gas was filtered by a heat and moisture exchange bacterial/viral filter and an additional simple bacterial/viral filter. In addition exhaust gas from the ventilators was scavenged.

It is important when assessing data and opinions on the effectiveness of each infection control measure to take into account the number of staff studied and the viral load to which they have been exposed. In order to adequately demonstrate the safety of a protective device a very large number of staff exposed to a significant viral load need to be studied. For example the results of a recent logistic regression study of the effectiveness of precautions which showed that both surgical and N95 masks were effective should be interpreted with great caution as the small number of infected staff included in the study precluded meaningful logistic regression analysis [7].

## Treatment

Treatment of SARS is controversial. The mainstay of treatment in Hong Kong has been a combination of an anti-viral, usually ribavirin, and corticosteroids [8,18]. Other treatments that have been tried have included immunoglobulin, convalescent serum from patients who have recovered from SARS and lopinavir-ritonavir. To date there are no controlled data to answer the question of whether any of these treatments are beneficial. The dosage regimes used at the Prince of Wales Hospital, were as follows. Ribavirin 8 mg/kg 8 hourly intravenously for 7-10 days followed by 4mg/kg enterally for another 11-14 days. The corticosteroid regime for severe cases was intravenous methylpred-

nisolone 10 mg/kg daily for 2 days followed by hydrocortisone 2 mg/kg 6 hourly. Repeated doses of methylprednisolone 10 mg/kg or 20 mg/kg per day were given if fever or chest X-ray changes persisted in the absence of obvious secondary bacterial infection, up to a cumulative dose of approximately 5g. A prophylactic broad spectrum antibiotic was given for a few days during and after pulses of methylprednisolone. Adverse effects of ribavirin include haemolytic anaemia, bone marrow suppression and teratogenesis. Although a high incidence of haemolytic anaemia has been reported [17], a higher dose was used. A case series from the Prince of Wales Hospital, Hong Kong reported no cases of haemolytic anaemia severe enough to require withdrawal of ribavirin but this study only reported data from the first two weeks of the illness [15]. Treatment at Tuen Mun Hospital evolved to use of lopinavir-ritonavir instead of ribavirin and use of lower doses of corticosteroids.

Supportive therapy centers on respiratory support. In view of the high incidence of ventilator associated pneumothoraces and pneumomediastinum we adopted a policy of intubating patients only when they desaturated below an arterial haemoglobin saturation of 90% when breathing high flow oxygen via a non-rebreathing mask. This approach is contraindicated in patients who are judged likely to be difficult to intubate or with significant cardiovascular failure as the risk of significant desaturation at the time of intubation is high. The safety of such an approach is also dependent on the immediate availability of medical staff who have a high level of experience of tracheal intubation. Our mechanical ventilatory strategy was based on the principles of ventilation for ARDS [19].

Cardiovascular support is based on the evidence that a restrictive fluid policy is preferable in ARDS [20] and the relatively low incidence and severity of non-respiratory organ failure. We adopted a restrictive fluid policy with active diuresis and the use of low doses of vasopressor and inotrope to provide cardiovascular support.

Management of complications of the disease and treatment includes a high level of vigilance for pneumothoraces and nosocomial bacterial sepsis. In selecting empirical antimicrobial therapy for nosocomial sepsis it should be borne in mind that patients with SARS may be colonized with different organisms than other critically ill patients. In our ICU *Pseudomonas aeruginosa* was almost never isolated during the three months of the SARS outbreak despite being a commonly

isolated organism beforehand while *Stenotrophomonas* species was much more commonly isolated.

## Prognosis

While the mortality of patients admitted to ICU is high (approximately 30-50% ICU mortality) [13,14]

the prognosis is probably no worse, and is possibly better than for other forms of pneumonia causing the same severity of illness. The presence of a high serum lactate dehydrogenase, hypoxia and a high absolute neutrophil count at the time of hospital admission, chronic hepatitis B infection, diabetes, male sex and higher age are associated with a worse outcome [8,9,11,17].

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