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CHAPTER 7

Severe Acute Respiratory Syndrome (SARS)

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Severe acute respiratory syndrome (SARS) is a viral pneumonia caused by a newly described coronavirus (SARS-CoV). During the SARS epidemic of November 2002 to July 2003, more than 8000 people in 26 countries on five continents were infected, of whom 774 lost their lives.[1] Sporadic, non–laboratory-associated cases of SARS have since been reported from southern China and highlight the possibility of repeated epidemics.

PATHOPHYSIOLOGY

SARS is the consequence of human infection with the SARS-CoV. SARS-CoV has been repeatedly isolated from the nasopharynx, respiratory secretions, feces, and blood of patients with SARS, and seroconversion has been consistently demonstrated in survivors.[2–4] Individuals with potential exposure to SARS cases, but who do not develop the clinical syndrome, generally do not show evidence of seroconversion.[5] Direct evidence of causation is provided by the observation that experimental infection of cynomolgus macaques with SARS-CoV results in a similar clinical and histologic respiratory disease to that observed in humans.[6] The causative link between the SARS-CoV and SARS has therefore been well established; however, the pathophysiologic mechanisms by which this syndrome occurs are less clear.

Clinical observation and histologic studies confirm that the pathologic effects of infection are largely, but not exclusively, confined to the respiratory tract. Bronchial epithelial denudation, loss of cilia, and squamous metaplasia occur early.[7] In lung tissue, an early phase of hyaline membrane formation, edema, and pneumocyte proliferation is followed by diffuse alveolar damage characterized by an exudative and proliferative phase.[7,8] Although these features appear similar to findings in acute respiratory distress syndrome (ARDS), characteristics such as predominant macrophage proliferation in consolidated areas and the presence of multinucleate giant cells are more specific for SARS and may suggest an important role for proinflammatory cytokines in the pathogenesis of SARS.[7] Some data suggest that the viral load in the respiratory secretions of patients with SARS is characterized by a peak occurring around the 10th day of illness followed by a decrease in viral load, concomitant with the appearance of an antibody response to the virus.[9] However, in most patients, clinical deterioration occurs progressively during the second week of illness despite a stable or decreasing viral load. This time course supports the suggestion that part of the lung damage may be immunopathologic.[8,9] Serum cytokine levels in patients with SARS have been measured. Observational data suggest that proinflammatory cytokines such as tumor necrosis factor and interleukin (IL)-6, IL-8, and IL-16 are increased and peak during the 8th to 14th day following illness onset.[10]

Diarrhea is the most commonly reported sign of gastrointestinal involvement reported in patients with SARS.[11] Viral particles have been detected in splenic tissue and the gastrointestinal tract[12]; however, no cytolytic damage or inflammatory change has been histologically demonstrated in the small or large bowel. Although subclinical myocardial diastolic dysfunction in patients with SARS has been described, histologic examination of cardiac muscle did not reveal any evidence of endocarditis, interstitial lymphocytic infiltrate, or myocardial cell necrosis.[13] The cause of the dysfunction

may be related to the effects of mechanical ventilation or circulating cytokines.

In summary, the pathophysiology of SARS remains obscure. The common presenting features (see later), many of which are similar to other viral infections, may be the consequence of viral replication, proinflammatory mediator production, or other as yet undiscovered mechanisms. The severe and largely isolated respiratory system manifestations typical of SARS are associated with evidence of both viral replication and proinflammatory mediator release, but exact pathophysiologic mechanisms are unknown. As has now been demonstrated in other infective conditions, it is also possible that genetic predisposition may play a role in determining the progression and ultimate severity of illness in individuals, but no published data as yet support this hypothesis.

CLINICAL PRESENTATION

Patients usually present with fever, chills, rigors, myalgia, and headache. A nonproductive cough is present in only approximately 50% of patients on presentation. Sore throat and rhinorrhea are infrequent (Fig. 7.1).[8] Common laboratory features include an elevated serum lactate dehydrogenase concentration, lymphopenia, hypocalcemia, and moderate thrombocytopenia.[8,14] The respiratory syndrome caused by SARS-CoV typically has an insidious onset. Although fever and other systemic symptoms may improve during the first week, particularly if anti-inflammatory therapy is used, the more important markers of clinical deterioration are progressive hypoxia and dyspnea, accompanied by the progression of pulmonary infiltrates on chest radiograph (Fig. 7.2).[8] Respiratory symptoms worsen slowly but steadily and reach a peak in the most severe cases during the first 10 to 15 days.[15] Published data consistently show that the time from symptom onset to intensive care unit (ICU) admission in these severe cases was approximately 8 to 10 days.[16–18] During the outbreak, approximately 20% to 30% of all patients with SARS required ICU admission.[8,9,14,16–19]

Admission to the ICU is almost always the consequence of progressive, severe respiratory failure. Current series reported an inability to maintain arterial oxygen saturation greater than 90% to 92% despite administration of supplemental oxygen at concentrations of more than 50% to 60% as criteria for admission to ICU

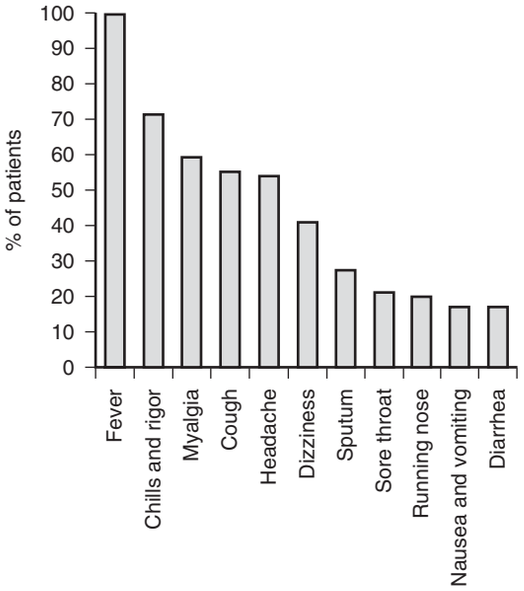

Figure 7.1 Frequency of distribution of symptoms of patients presenting with severe acute respiratory syndrome (SARS). (Adapted from Lee N, Hui D, Wu A, et al: A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1986–1994.)

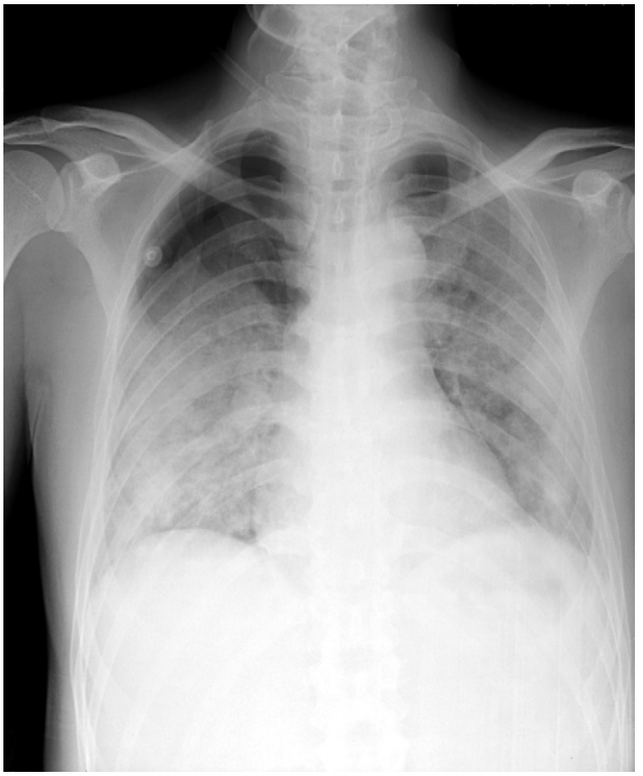

Figure 7.2 Chest radiograph showing bilateral heterogeneous consolidation in both lungs in a 47-year-old male patient with severe acute respiratory syndrome (SARS). The patient has a small, spontaneous right pneumothorax. No pleural effusion or cardiomegaly is seen.

for monitoring. In the currently reported ICU series, more than 90% of patients met the clinical criteria of ARDS following admission (acute onset of bilateral diffuse pulmonary infiltrates on chest radiograph, a ratio of arterial oxygen tension to fractional inspired oxygen concentration (Pa_{O_2}/Fi_{O_2}) of less than 200 mm Hg, and the absence of left atrial hypertension[20]).[16–18] Median Acute Physiology and Chronic Health Evaluation (APACHE) II scores were reported to range between 11 and 19.5, and most patients had isolated respiratory failure on admission.[16–18]

DIAGNOSIS

During the early outbreak, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) criteria, comprising clinical, epidemiologic, and laboratory features for the diagnosis of SARS, were successfully used.[21] Briefly, these criteria were as follows. Patients demonstrating the clinical features of a temperature higher than 38°C and one or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia), as well as the epidemiologic features of travel within 10 days of onset of symptoms to an area with current suspected community transmission of SARS, or close contact within 10 days of onset of symptoms with a person known or suspected to have SARS, were considered suspect cases. Probable cases were defined as those having the foregoing features, as well as evidence of pneumonia on a chest radiograph or computed tomography scan. Because of the variable performance of laboratory testing for SARS at this time, case classification did not rely on laboratory criteria.

Currently, in the absence of an outbreak and endemic areas, epidemiologic criteria are of very limited use in assisting diagnosis. Only specific epidemiologic criteria, such as a history of laboratory exposure to the SARS virus, remain important. The current laboratory diagnostic criteria from the CDC are therefore important and stringent. They require the detection of antibody to SARS-CoV in a serum sample, or the detection of SARS-CoV RNA by reverse transcriptase–polymerase chain reaction (RT-PCR) in two samples, or the isolation of SARS-CoV with confirmation by a PCR assay or the isolation of SARS-CoV.[22] Findings must be verified in an appropriate WHO-certified laboratory. The use of RT-PCR is problematic, however, because interpretation requires some understanding of test parameters. Peiris and colleagues found that the sensitivity of RT-PCR assay is highly dependent on the type of specimen tested and the time of collection of specimens with respect to the day of onset of symptoms.[9] In particular, the viral load as detected by RT-PCR seems to follow a triphasic pattern with a peak on day 10. Sensitivity for respiratory specimens collected at presentation is low (32%), but it increases to approximately 70% during the second week. Yam and associates found that the sensitivities of RT-PCR performed on nasopharyngeal specimens and throat swabs collected between day 1 and day 5 after admission were 61% to 68% and 65% to 72%, respectively.[23] However, repeated testing on respiratory specimens increases sensitivity to 75% to 79%. The sensitivities on urine and fecal specimens collected between day 5 and day 10 after admission are lower (50% to 60%). The optimal strategy in using RT-PCR assay remains to be defined.

The risk of false-positive results from SARS-CoV testing remains high given the current low prevalence of the disease. The burden on the health care system for contact tracing and isolation of patients with false-positive results can be significant. The WHO currently recommends SARS-CoV testing in low-risk areas *only* when there is clustering of cases fulfilling the clinical case definition of SARS in an acute care facility within the same 10-day period of onset of illness or in cases epidemiologically linked to a laboratory where specimens of SARS-CoV are handled. Routine testing of SARS-CoV in cases of atypical pneumonia unexplained by another cause is reserved for areas of potential reemergence of the infection such as Guandong in southern China.

The absence of antibody to SARS-CoV in a convalescent-phase serum sample obtained more than 28 days after symptom onset is recommended for exclusion of probable and suspected cases of SARS. With serologic tests, there is also the possibility of cross-reactions among coronaviruses.[24] Although seroconversion may occur earlier, it is not useful for diagnosing or excluding acute disease; therefore, RT-PCR assay, albeit less than ideal, remains the best current method of detecting early clinical infection.

VENTILATORY SUPPORT AND OUTCOME

Several studies have identified prognostic factors for ICU admission. These include older age (especially patients >60 years), the presence of comorbidities (particularly diabetes mellitus and hepatic or cardiac disease), and elevated lactate dehydrogenase levels on admission to the hospital.[13,14,25] The treatment of patients admitted to the ICU is mainly confined to routine organ support; beyond routine organ support protocols, the medical therapy of patients with SARS is controversial. Although antiviral agents were extensively used in reported series,

clinical data supporting the efficacy of these agents are lacking.[26–28] Anti-inflammatory therapy and immunomodulation with steroids, particularly high-dose methylprednisolone, have been used, and although observational data in SARS suggest that high-dose methylprednisolone may be helpful in modulating the lung injury,[18,29–32] no high-quality outcome data support their use. The use of steroids for the treatment of ARDS in general remains controversial.[33–35] High-dose methylprednisolone may also potentially cause serious side effects, notably osteonecrosis, which can have significant long-term debilitating effects.[15] Intravenous immunoglobulin, immunoglobulin M–enriched immunoglobulin, and plasma from patients in the convalescent phase have been used in critically ill patients with SARS; however, clinical efficacy is unproven.

Severe hypoxia or the development of respiratory exhaustion leads to mechanical ventilation in 50% to 85% of patients admitted to the ICU.[16–18] Based on the similarity of the clinical,[13,14, 16–18] radiologic,[36] and pathologic[7,13] features, the severe hypoxemic respiratory failure associated with SARS-CoV infection appears to resemble other forms of ARDS. It therefore appears prudent to use a currently accepted ventilation strategy for patients with ARDS.[37,38] Such a strategy to minimize ventilator-associated lung injury and to improve mortality includes ventilation with low tidal volumes, 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.[39,40] All reported ICU studies to date have documented attempts to limit tidal volume to 6 to 8 mL/kg estimated lean body weight, to limit the plateau or peak airway pressure to less than 30 to 35 cm H_2O, to titrate PEEP to minimize the inspired oxygen concentration, and to target moderate arterial oxygen saturation (88% to 95%) while allowing the arterial partial pressure of carbon dioxide ($PaCO_2$) to rise if necessary, provided the pH is greater than 7.15.

Prone position ventilation is a technique that often improves oxygenation in ARDS.[41] Although one large, randomized, controlled trial of prone ventilation showed no improvement in mortality or organ dysfunction overall, this approach may be of benefit in more severely ill patients.[42] Prone ventilation was utilized to a varying degree in mechanically ventilated patients with SARS; however, not enough data are available to draw any conclusions regarding efficacy.[16–18] In our unit, the experience with prone ventilation was one of extreme interpatient variability in response (determined by improved oxygenation in the prone position). The use of nitric oxide in ARDS has not been shown to improve outcome, and anecdotally, the experience in Toronto and Singapore also demonstrates little benefit from nitric oxide in patients with SARS.[16,17]

Few data on noninvasive positive pressure ventilation in SARS have yet been reported, but it is our opinion that this mode of ventilation be avoided because of the risk of infected aerosol generation from inevitable mask leakage and high gas-flow compensation.[18,43] An unexpectedly high incidence of barotrauma-related air leak has been reported in patients with SARS. Pneumothorax, pneumomediastinum, and subcutaneous emphysema, alone or in combination, occurred in 20% and 30% of patients admitted to ICU.[16–18] This incidence is high compared with rates previously reported in ARDS.[39,44] The risk does not seem to be associated with the use of excessive tidal volume or airway pressure,[16,18] and it is not limited to patients receiving mechanical ventilation.[18] 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,[45] and rupture of these cysts during or after formation could contribute to extraparenchymal gas leaks.

Data from the ICU patients of one cohort showed an association between more negative average 24-hour fluid balance and good outcome.[18] This finding corresponds with those in ARDS of non-SARS origin in which some evidence indicates that restrictive fluid management is associated with better oxygenation, lower mortality, and fewer patient ventilator days.[46,47] Causation is not proved, 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.

Nosocomial infections are an expected complication, and in the Singapore series, 12 of 46 patients (26%) developed positive blood cultures.[17] In our unit, we observed a high incidence of ventilator-associated pneumonia (37 episodes per 1000 ventilator days) and a high incidence of methicillin-resistant *Staphylococcus aureus* acquisition within the ICU (about 25% of SARS admissions). Possible contributing factors included the use of steroids, an increase in the use of prophylactic and preemptive antibiotics, prolonged mechanical ventilation, and the routine use of gloves and gowns, which have been shown to be associated with poor hand hygiene compliance.

ICU admission carries a high mortality rate. For patients with SARS who were admitted to the ICU, the 28-day 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).[16–18] Longer follow-up showed a slightly higher mortality.[17] Patients who died were more often older, had higher APACHE II scores, had greater comorbidities, and were more likely

to have had bilateral radiologic infiltrates on hospital admission.[16,18] 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.[15]

In a six-month follow up study of a cohort of SARS patients, exercise capacity and health status of SARS survivors was considerably lower than that of a normal population at 6 months.[48] Most pulmonary function test parameters were minimally impaired, although significant impairment in surface area for gas exchange was noted in 15.5% of survivors. The functional disability appeared disproportionate to the degree of lung function impairment and may have been related to additional factors such as muscle deconditioning and steroid myopathy. Lung function tests at 6 months showed moderate, but significantly lower forced vital capacity (FVC), total lung capacity (TLC), and carbon monoxide transfer factor (TLCO) in survivors who had required ICU support than in those who were treated on general wards, although no significant differences were noted in 6MWD and respiratory muscle strength.[48]

A striking feature during the epidemic was its high rate of nosocomial transmission of SARS, particularly to health care workers.[1] In addition to the risk from direct patient exposure, many procedures in the ICU, such as intubation, bronchoscopy, or the use of nebulizers and Venturi-type oxygen masks, pose an additional risk of transmission of SARS-CoV to the health care worker. Because the disease has the ability to produce significant morbidity and to incapacitate staff for long periods, staff protection is critical to ensure the continued provision of adequate ICU services. The CDC issued guidelines and recommendations on infection control in health care facilities.[49] It is considered prudent by some clinicians to adopt contact and airborne infection isolation precautions, in addition to standard precautions.[50,51] Patient isolation in rooms with appropriate air-change performance,[52] as well as the appropriate and strictly enforced use of gloves and gowns, particulate, respirators and eye protection, is required.[49–51,53]

Ventilator circuits should be isolated from the environment by the use of filters, scavenging, and closed-suction systems, for example. Environmental cleansing with appropriate solutions such as chloride and hypochlorite is an important component of infection control. Staff members should be fully informed regarding relevant advances in knowledge of SARS and properly educated on infection control precautions.[53] Psychological support should be offered to the staff.

Critical care resources can be significantly strained during a SARS outbreak, as a result of an influx of patients with SARS, the closing of institutions for quarantine, and illness or quarantine of health care workers.[16] One important lesson learned from SARS is that prospective local and regional contingency planning for major infectious disease outbreaks is critical if adequate ICU services are to be maintained.[50]

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