

Severe acute respiratory syndrome

Jann-Tay Wang and Shan-Chwen Chang

Purpose of review

Severe acute respiratory syndrome (SARS) is an infectious disease first recognized in November 2002 in Guangdong Province, China. It spread to many countries all over the world during February to June 2003, with 8098 cases reported. Twenty-one percent of the affected people were health care workers. Because SARS is a new emerging disease, this review describes the current understanding about the etiology, clinical pictures, laboratory and radiological findings of SARS.

Recent findings

Severe acute respiratory syndrome-associated coronavirus (SARS-CoV) was quickly found to be the etiological agent of SARS in April 2003. The transmission of SARS-CoV between human beings is mainly due to close contact. Using barrier precautions, the transmission of SARS-CoV can be prevented. The most common clinical presentations of patients with SARS include fever, cough, and dyspnea. The common laboratory findings include lymphopenia, thrombocytopenia, elevated serum alanine and aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, and C-reactive protein. The most common radiological finding is pneumonic lesion(s) in the chest radiogram. Many patients experience exacerbation of clinical symptoms in the second week of disease course and some may progress to respiratory failure and need mechanical ventilatory support. The overall case fatality rate is 9.6%. The current method of treatment of SARS is still controversial.

Summary

SARS is an infectious disease with high contagiousness and a high mortality rate. Early case identification and infection control are two important factors to limit its spread.

Keywords

severe acute respiratory syndrome, coronavirus, SARS-associated coronavirus

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Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Correspondence to Dr Shan-Chwen Chang, Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, No. 7 Chung-Shan South Road, Taipei 100, Taiwan
Tel: +886 2 23970800 ext 5401; fax: +886 2 23971412;
e-mail: sc4030@ha.mc.ntu.edu.tw

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Abbreviations

CT	computed tomography
HCW	health care worker
LDH	lactate dehydrogenase
RT-PCR	reverse-transcriptase polymerase chain reaction
SARS	severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus

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Introduction

Severe acute respiratory syndrome (SARS) is a new infectious disease in humans. The first noted victim of SARS was a businessman from the city of Foshan in Guangdong Province, China [1]. Information about the first patient and many others, however, was not released to other countries until February 2003, when SARS was transported to Hong Kong and then to Vietnam, Singapore, Canada, and many other countries. Thereafter, SARS spread rapidly around the world, with 8098 cases reported as of July 2003 [2]. SARS is a life-threatening and highly contagious respiratory illness with a high propensity to spread to health care workers (HCWs) and household members. Facing this new emerging infectious disease, the global medical community has achieved an unprecedented speed of progress in understanding SARS during the past several months. Here we review the current knowledge about the etiology, clinical pictures, laboratory and radiological findings, treatment strategies, and infection control measures for SARS.

Etiology

Peiris *et al.* [3**] first described the etiologic link between a coronavirus and the SARS epidemic in Hong Kong. In 45 out of 50 SARS patients, one or more laboratory tests [32 by serology testing, 22 by reverse-transcriptase polymerase chain reaction (RT-PCR) testing, and two by virus culture] suggested that the coronavirus is the etiology of SARS. This finding was rapidly confirmed by following studies [4**,5**]. Using phylogenetic analyses and comparisons of genomic sequences, the novel coronavirus, SARS-associated coronavirus (SARS-CoV), was found to be only moderately related to two previously characterized human coronaviruses, HCoV-OC43 and HCoV-229E [6,7].

The coronavirus is a diverse group of large, enveloped, positive-stranded RNA viruses belonged to the genus *Coronavirus*. The previously known animal coronavirus can cause various respiratory and gastrointestinal diseases in animals. The previously known human coronavirus is a major cause of the common cold and can occasionally cause pneumonia in humans.

The origin of SARS-CoV is still controversial. Rota *et al.* [6] claimed that the SARS-CoV genomic sequence does not provide obvious clues concerning the potential animal origin. Guan *et al.* [8*], however, found SARS-CoV-like viruses isolated from palm civets and raccoon dogs and Yu *et al.* [9*] found a higher prevalence of IgG

antibody to SARS-CoV in animal traders, especially those dealing with masked palm civets, wild boars, muntjac deer, hares, and pheasant. These studies suggest the possibility of animal origin, animal reservoir, and interspecies transmission of SARS-CoV. Further studies are needed, however, to clarify the origin and animal reservoir of SARS-CoV.

Transmission

At the time of writing, the available evidence suggests that SARS-CoV appears to be transmitted primarily by droplets and by direct contact [10]. Hence, household member of SARS patients as well as HCWs caring for SARS patients are at greatest risk of contracting SARS. Droplet and contact precautions have been shown to be effective in prevention of nosocomial transmission of SARS [11•].

In addition to airway secretions, SARS-CoV can also be found in the stools, urine, and blood of SARS patients [12••]. Because of the presence of virus in the stools, some authors have suggested the possibility of a fecal-oral route of transmission. The SARS-CoV is stable in stools at room temperature for at least 1–2 days and more stable, for up to 4 days, in the stools of patients with diarrhea [13]. The epidemiological investigation of an outbreak of SARS in the Amoy Gardens in Hong Kong suggested that the outbreak may have been caused by a faulty sewage system [14]. This outbreak raised the possibility of an environmental source of infection.

Peiris *et al.* [12••] studied the sequential viral load of SARS-CoV in the nasopharyngeal aspirate from 14 SARS patients. The viral load in nasopharyngeal aspirate was found to increase gradually, peaking on the 10th day after onset of symptoms, and then decreasing gradually. This finding suggests that SARS patients may be most contagious around the 10th day of the disease. However, further clarification is needed on the actual time points of transmission of the SARS-CoV during the disease course and when the SARS-CoV can be transmitted most efficiently. With our accumulated knowledge of SARS and SARS-CoV, we will be able to address these important issues in the future.

Clinical features

The incubation period of SARS is typically 2–7 days, however isolated reports have suggested an incubation period as long as 10 days [15]. The male to female ratio is about 0.87 [2], which may be because HCWs account for 21% of all patients affected by SARS and most HCWs are female nurses. The majority of SARS patients are adults and only a few of them are children aged 15 years or younger [15,16•]. Fever (over 38.0°C) occurs in nearly all patients, in some cases being absent in elderly or critically ill patients, and is often the first symptom

[12••,15,17•,18,19]. Fever is usually high, sometimes associated with chills. Other early manifestations include headache, malaise, and myalgia. Cough, dyspnea, and diarrhea have also been reported to be the first symptoms in some patients [18]. The presence of rhinorrhea alone, however, suggests that the diagnosis is unlikely to be SARS [18]. Typically, skin rash, lymphadenopathy, and neurologic findings are absent at initial presentation. The common symptoms of SARS patients seen at their presentation are listed in Table 1.

After 3–7 days, a lower respiratory phase begins with the onset of a dry, nonproductive cough or dyspnea. This may progress to hypoxemia. The lower respiratory phase usually resolves in the third week of disease. In 10–20% of cases, however, the respiratory illness becomes severe enough to require mechanical ventilatory support and progresses into acute respiratory distress syndrome in the second to third week of the disease.

A biphasic course of SARS has been described in many patients, with an initial illness followed by improvement and then subsequent deterioration. This deterioration can present as recurrent fever 4–7 days after initial defervescence, new infiltrates in chest radiographs, respiratory failure, or watery diarrhea [12••]. Serial quantitative RT-PCR tests of nasopharyngeal aspirate in 14 patients with this kind of subsequent deterioration reveal that peak viral loads occur at day 10 after onset of illness [12••]. This suggests that the early symptoms in week one of the disease, when increasing viral loads are noted, may be largely related to the effect of viral replication and the so-called ‘subsequent deterioration’ in week two may be due to the host immune response rather than uncontrolled viral replication.

Asymptomatic SARS-CoV infection, confirmed by seroconversion for SARS-CoV antibody, has also been described [9•,20]. We still do not know why a person infected with SARS-CoV has no typical symptoms, and the reason for the infectivity of an asymptomatic person.

Table 1. Common symptoms of the severe acute respiratory syndrome patient at presentation

Symptoms	Frequency (%)
Fever	99.3–100
Chills or rigor	27.8–73.2
Myalgia	49.3–68.0
Cough	29.0–74.3
Headache	15.0–55.8
Dizziness	4.2–44.8
Sputum production	4.9–29.0
Sore throat	11.0–23.2
Rhinorrhea	0–2.1
Diarrhea	1–23.6

The case fatality rates of SARS reported from different areas range from 7% to 17% [2]. Different patient populations and the availability of medical care may be the main reasons for these variations. The fatality rate of SARS patients needing mechanical ventilatory support is about 50% [18]. The reported independent factors predictive for mortality in SARS patients include advanced age (especially those aged over 60 years), underlying comorbidities (such as diabetes, cardiovascular disease, cancer, chronic obstructive pulmonary disease), high lactate dehydrogenase (LDH) level on presentation, neutrophilia on presentation, high peak LDH level, and SARS-CoV positive nasopharyngeal aspirate [17,18,21,22].

The complications of SARS need further discussion. Rhabdomyolysis and hemophagocytosis have been reported to be possible complications associated with SARS [23,24]. More data are needed, however, to discover the whole picture.

Laboratory findings

Laboratory findings in SARS patients include thrombocytopenia, leukopenia (in particular lymphopenia), elevated LDH, elevated C-reactive protein, elevated alanine or aspartate aminotransferase, and elevated creatine phosphokinase [15,17,18,19]. Hyponatremia, hypokalemia, hypocalcemia, prolonged activated partial thromboplastin time, and elevated D-dimer level are also noted in some patients. Renal function and prothrombin time, however, remain normal in most SARS patients.

Radiological findings

The initial chest radiograph of SARS patients may be normal or show ground-glass opacities, patchy consolidation, and diffuse small nodular opacities, often with a peripheral distribution [15,18,25,26]. Pneumomediastinum can be seen in some patients. Pleural effusion, hilar lymphadenopathy, and cavitation are usually absent in SARS patients. Seven to ten days after presentation, chest radiographs are found to gradually deteriorate in most SARS patients, followed by improvement. Some patients have fluctuating chest radiographic findings; shifting lesions may appear for a time and recover later. Some patients have static chest radiographic findings for some time followed by improvement. Others have progressive deterioration, which may rapidly lead to death [25,26].

The early findings on chest radiographs may be subtle. Computed tomography (CT) scanning is more sensitive than plain films in detecting early pulmonary lesions. High-resolution CT scans may demonstrate abnormalities in patients with suspected SARS who have normal findings on plain chest radiographs [18]. The characteristic CT findings are either areas of ground-glass

infiltrates or consolidation, or a mixture of both [25,26]. None of the CT findings are specific.

Diagnosis

Laboratory methods for diagnosis of SARS-CoV infection include isolation of SARS-CoV from clinical specimens, the RT-PCR test specific for SARS-CoV, and seroconversion of antibody for SARS-CoV [27].

The clinical specimens eligible for the RT-PCR assay for SARS-CoV include respiratory secretion (in particular nasopharyngeal aspirate), stool, urine, blood, and lung tissues. A confirmed positive RT-PCR result for SARS-CoV should fulfill any one of the following criteria: (1) at least two different clinical specimens are positive; or (2) the same clinical specimen collected on two or more occasions during the course of the illness is positive; or (3) two different assays or repeat RT-PCR tests using the original clinical sample on each occasion of testing are both positive. The sensitivity of RT-PCR depends on the timing of specimen collection [12]. For nasopharyngeal aspirate, the sensitivity rates increase within the first 2 weeks after onset of illness (from 32% on day 3 up to 68% on day 14). It is also reported that in stool samples collected from SARS patients on day 14 after onset of illness, the viral RNA can be detected in 97% of patients. Therefore, testing of multiple nasopharyngeal and fecal samples will increase the sensitivity of the RT-PCR assay and a negative result of RT-PCR assay for SARS-CoV does not exclude the diagnosis of SARS completely.

Seroconversion for SARS-CoV antibody is confirmed either by a negative antibody test on acute serum followed by a positive antibody test on convalescent serum or fourfold or greater rise in antibody titer between acute and convalescent sera tested in parallel [27]. Serologic testing for SARS-CoV antibody consists of immunofluorescent assay and enzyme-linked immunosorbent assay. Patients with SARS seem to begin to seroconvert on the 10th day after onset of symptoms [12].

Other common causes of respiratory illnesses should also be considered and excluded. Therefore, other laboratory diagnostic tests such as blood culture, sputum Gram stain and culture, and testing for influenza A, influenza B, parainfluenza, respiratory syncytial virus, adenovirus, *Mycoplasma pneumoniae*, *Chlamydiae*, as well as *Legionella* should be performed based on the clinical evaluation.

Treatment

There is still no specific treatment currently available for SARS. Supportive care plays an important role at the present time. Because the etiological diagnosis is generally unclear initially, empirical antibiotics for the treatment of community acquired pneumonia with coverage of atypical pathogens are usually recommended

[28]. So *et al.* [29^{*}] proposed a treatment protocol for SARS with the emphasis on the combination of an antiviral agent, ribavirin, and methylprednisolone. Ribavirin is a broad-spectrum antiviral agent, especially against RNA virus. However, there is no direct clinical evidence suggesting the efficacy of ribavirin in the treatment of SARS [17^{*},18]. *In vitro*, it has been demonstrated that ribavirin affects the replication of SARS-CoV only in very high concentrations, which are unachievable in the human body [30]. The role of ribavirin in the treatment of SARS is questionable.

Some reports suggest that corticosteroids may be beneficial, particularly in patients with progressive pulmonary infiltrates [12^{**},17^{*},18]. Findings that pulmonary infiltrates progress with decreasing viral load [12^{**}], the similarity of abnormalities revealed by CT scans of SARS patients to bronchiolitis obliterans with organizing pneumonia [17^{*}], and cytokine deposition in destructed lung tissue [25] also indirectly suggest the potential role of corticosteroids in the treatment of SARS. Various regimens, however, have been used in different centers, with dosages of methylprednisolone ranging from 40 mg twice daily to 2 mg/kg per day to pulse doses of 500 mg intravenously per day [17^{*},18]. Further studies are needed to ascertain whether patients receiving corticosteroid therapy have a better prognosis and, if so, what is the optimal regimen, dosage, and timing of administering the steroids.

At the time of writing, several other compounds, including interferons, aminopeptidase N inhibitors, glycyrrhizin and lopinavir/ritonavir, have been proposed as potential treatment regimens for SARS [30–34]. Loufty *et al.* [33] reported their preliminary experience about using the combination of interferon alfacon-1 and corticosteroid to treat nine SARS patients. With the comparison of using corticosteroid alone, interferon alfacon-1, a synthetic interferon alfa, plus corticosteroid was associated with reduced disease-associated impaired oxygen saturation, more rapid resolution of radiographic lung abnormalities, and lower levels of creatine kinase. Chen *et al.* [29^{*}] conducted a retrospective matched cohort study to evaluate the efficacy of lopinavir/ritonavir in the treatment of SARS. In that study, the addition of lopinavir/ritonavir to a standard treatment protocol as an initial treatment for SARS appeared to be associated with improved clinical outcome [34]. Further evaluation is needed, however, to confirm their efficacy.

Infection control

Early identification and isolation of SARS patients is important to prevent spread of the disease. Several infection control measures have been recommended for this purpose.

To identify patients with SARS, patients presenting to health care facilities should be screened with targeted questions as soon as possible after arrival, ascertaining details on fever, respiratory symptoms, contact history with a SARS patient, travel history, and residential setting. After the initial screening, suspected SARS patients should be subject to isolation precautions suggested for SARS unless a definite diagnosis other than SARS is established [35]. Although previous studies have demonstrated that contact and droplet precautions are effective to control the transmission of SARS, some experts prefer to apply airborne, instead of droplet, precautions to SARS patients [36]. Therefore, SARS patients who stay in hospital should be put on contact and droplet or, if feasible, airborne precautions. Visitors to the SARS patients are not allowed in most hospitals. Procedures resulting in coughing and aerosolization of respiratory secretions and noninvasive positive pressure ventilation (e.g. continuous positive airway pressure, bi-level positive airway pressure) should be avoided. If SARS patients experience respiratory failure and are intubated, sputum suction performed in a close system is recommended [36].

It is recommended that SARS patients managed as outpatients should wear a surgical mask in the presence of household members, limit their interactions outside the home, and wash their hands frequently with soap and water or alcohol-based handrubs [36,37]. Household members in contact with patients are advised to wash their hands frequently and carefully, to wear disposable gloves for any direct contact with body fluids from the patient, to remove the gloves and then wash their hands immediately after any contact, and not to share eating utensils, towels, and bedding with the patient [37].

An important feature of the global outbreak of SARS is that many HCWs caring for SARS patients develop the infection, accounting for 21% of all SARS patients [2]. It has been suggested, therefore, that surveillance for fever and respiratory symptoms should be conducted in all HCWs in direct contact with SARS patients, as well as those who may have come into contact with the body fluids of SARS patients or the environment surrounding SARS patients, especially those with unprotected exposure [38]. Because the incubation period of SARS may be as long as 10 days, surveillance is recommended for up to 10 days after the last contact or exposure. HCWs developing fever or respiratory symptoms within 10 days following the last exposure are asked to use infection control precautions to minimize the potential for transmission and to seek health care evaluation.

Conclusion

SARS is a new emerging infectious disease that can affect HCWs and for which there is currently no

specific treatment. Early case identification and infection control are two important factors to limit its spread. Further studies focusing on the pathogenesis, transmission route, host susceptibility, and treatment of the infection are needed, along with a vaccine development program.

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