Severe Acute Respiratory Syndrome
Pertinent Clinical Characteristics and Therapy

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Abstract

Severe acute respiratory syndrome (SARS) is a newly emerged infection that is caused by a previously unrecognized virus – a novel coronavirus designated as SARS-associated coronavirus (SARS-CoV). From November 2002 to July 2003 the cumulative number of worldwide cases was >8000, with a mortality rate of close to 10%. The mortality has been higher in older patients and those with co-morbidities. SARS has been defined using clinical and epidemiological criteria and cases are considered laboratory-confirmed if SARS coronavirus is isolated, if antibody to SARS coronavirus is detected, or if a polymerase chain reaction test by appropriate criteria is positive. At the time of writing (24 May 2004), no specific therapy has been recommended. A variety of treatments have been attempted, but there are no controlled data. Most patients have been treated throughout the illness with broad-spectrum antimicrobials, supplemental oxygen, intravenous fluids, and other supportive measures. Transmission of SARS is facilitated by close contact with patients with symptomatic infection. The majority of cases have been reported among healthcare providers and family members of SARS patients. Since SARS-CoV is contagious, measures for prevention center on avoidance of exposure, and infection control strategies for suspected cases and contacts. This includes standard precautions (hand hygiene), contact precautions (gowns, goggles, gloves) and airborne precautions (negative pressure rooms and high efficiency masks). In light of reports of new cases identified during the winter of 2003–4 in China, it seems possible that SARS will be an important cause of pneumonia in the future, and the screening of outpatients at risk for SARS may become part of the pneumonia evaluation.

1. Definition

For surveillance purposes and before the availability of laboratory tests to detect the causative agent, SARS was originally defined using clinical and epidemiologic criteria from suspect or probable cases.¹¹ A suspect case included a respiratory illness of unknown etiology and with the following criteria:
- measured temperature >100.4°F (>38.0°C)
- one or more clinical findings of respiratory illness (e.g. cough, shortness of breath, difficulty in breathing, or hypoxia)
- travel within 10 days of onset of symptoms to an area with suspected or documented community transmission of SARS (excluding areas with secondary cases limited to healthcare workers or direct household contacts and close contact within 10 days of onset of symptoms with either a person with a
respiratory illness or a person under investigation or suspected of having SARS).

A probable case was defined as a suspect case with either radiographic evidence of pneumonia or respiratory distress syndrome, or autopsy findings consistent with respiratory distress syndrome without an identifiable cause.\(^{[4]}\)

Once the virus was identified and laboratory tests became available for detection, the surveillance case definition for SARS was updated to include laboratory criteria for evidence of infection with the SARS-associated coronavirus (SARS-CoV). Initially, since it was unclear whether SARS infection could be present in people who were asymptomatic, the definition included the possibility of asymptomatic (‘subclinical’) infection. However, subsequent investigations suggest that asymptomatic infection is very uncommon.\(^{[1]}\) As a consequence, the latest surveillance case definition for SARS by the US Center for Disease Control and Prevention (CDC) has been updated to include clinical criteria for early illness, mild-to-moderate illness, and severe respiratory illness, which are then characterized by epidemiological and laboratory criteria (table I).\(^{[5]}\)

### 2. Etiology

Soon after the recognition of the clinical syndrome of SARS, several different laboratories identified a novel coronavirus, designated SARS-CoV, in Vero E6 cell cultures inoculated with respiratory secretions and lung tissue of infected patients.\(^{[6,7]}\) Other techniques, including electron microscopy, reverse transcription-polymerase chain reaction (RT-PCR), and seroconversion, have also pointed to this as the causative agent. Sero-epidemiological data indicate the SARS-CoV was not previously found in humans.\(^{[8]}\) Preliminary reports of detection of the SARS coronavirus in Himalayan palm civet cats and a number of other species are suggestive of interspecies transmission of this new virus. Investigators from Hong Kong reported a coronavirus resembling SARS virus isolated from several Himalayan palm civet cats and a raccoon dog obtained in a market in the Guangdong province (such animals are considered as food delicacies in that region).\(^{[9]}\) They also reported that several of the handlers at the market had antibody to the SARS virus. Studies of the genetic sequence of the two viruses show a similar pattern, suggesting a species jump from wild animals to humans. Furthermore, experimental infection of macaques with SARS-CoV produced a pneumonia that was pathologically similar to SARS in humans.\(^{[10]}\) Stavrinides and Guttman compared the SARS-CoV genome with related coronaviruses and found about half the DNA resembled coronavirus sequences from mammals, while the other half looked like virus found in birds.\(^{[11]}\) These data suggest a possible past recombination event between mammalian-like and avian-like parent viruses which may have been responsible for the switch of host of the SARS-CoV from animals to humans.

### 3. Epidemiology

As of July 2003 the cumulative number of worldwide SARS cases was 8437, with a mortality of 9.6%.\(^{[12]}\) Of the reported cases 64% were from China, 19% from Hong Kong, 8% from Taiwan, 3% from Canada, and 2% from Singapore. The US has been relatively spared from the clinical impact of SARS. At July 2003, 27 probable cases had been reported, of which only eight had laboratory confirmation of acute coronavirus infection.\(^{[13]}\)

The initial cases reported in Hong Kong were linked to an index patient, a medical doctor from the Guangdong province of China who traveled to Hong Kong to attend a wedding in late February 2003.\(^{[14]}\) He had previously treated patients with ‘atypical’ pneumonia in Guangdong. Subsequently several guests who had stayed at the same hotel became ill with SARS. These patients subsequently infected numerous healthcare workers and family members or became index cases in other countries (Canada, Vietnam, Singapore, etc.) [figure 1].

The mortality has been higher in older patients and those with co-morbidities. The syndrome has been observed primarily in adults aged 25–70 years, and children have been relatively spared. There appears to be no significant underlying predisposing condition for the development of SARS, however the elderly and patients with underlying conditions are at greater risk for mortality. In one study from Hong Kong the mortality for those >60 years of age was 43%,\(^{[15]}\) In another study, multivariate analysis showed that age >60 years, presence of diabetes mellitus or heart disease, and the presence of other co-morbid conditions were independently associated with mortality.\(^{[16]}\) Early in the evaluation of this syndrome, most of the descriptions were of patients who required hospitalization. However, as more cases were identified, particularly in the Western countries, the majority of patients have not required hospitalization.

SARS appears to be transmitted by close contact with patients who have illness due to SARS virus.\(^{[1,2]}\) The greatest risk of transmission is most probably via direct contact with respiratory secretions. There is no evidence of spread from patients before they develop symptoms. The majority of cases have been reported among healthcare workers and family members of affected persons. However, evidence of community spread of the disease is emerging, suggesting that other modes of transmission, such as airborne or direct contact, may also have a role.\(^{[1]}\) Clusters of cases in community settings such as hotels and apartment buildings demonstrate that transmission can be efficient. Many household
Table I. Updated (12 December 2003) US surveillance case definition for severe acute respiratory syndrome (SARS) [5]

Clinical criteria

**Early illness**
Presence of two or more of the following features: fever (might be subjective), chills, rigors, myalgia, headache, diarrhea, sore throat, or rhinorrhea

**Mild-to-moderate respiratory illness**
Temperature >100.4°F (>38°C), and

One or more clinical findings of lower respiratory illness (e.g. cough, shortness of breath, or difficulty breathing)

**Severe respiratory illness**
Meets clinical criteria of mild-to-moderate respiratory illness, and

One of more of the following findings:
- radiographic evidence of pneumonia, or
- acute respiratory distress syndrome, or
- autopsy findings consistent with pneumonia or acute respiratory distress syndrome without an identifiable cause

Epidemiologic criteria

**Possible exposure to SARS-CoV**
One or more of the following exposures in the 10 days before onset of symptoms:
- travel to a foreign or domestic location with documented or suspected recent transmission of SARS-CoV, or
- close contact with a person with mild-to-moderate or severe respiratory illness and history of travel in the 10 days before onset of symptoms to a foreign or domestic location with documented or suspected recent transmission of SARS-CoV

**Likely exposure to SARS-CoV**
One or more of the following exposures in the 10 days before onset of symptoms:
- close contact with a person with confirmed SARS-CoV disease, or
- close contact with a person with mild-to-moderate or severe respiratory illness for whom a chain of transmission can be linked to a confirmed case of SARS-CoV disease in the 10 days before onset of symptoms

Laboratory criteria

**General criteria**
Detection of serum antibody to SARS-CoV by a test validated by CDC (e.g. enzyme immunoassay), or
Isolation in cell culture of SARS-CoV from a clinical specimen, or
Detection of SARS-CoV RNA by a RT-PCR test validated by CDC and with subsequent confirmation in a reference laboratory (e.g. CDC)

**Case classification**

*SARS-CoV disease*

**Probable case of SARS-CoV disease:** meets the clinical criteria for severe respiratory illness and the epidemiologic criteria for likely exposure to SARS-CoV

**Confirmed case of SARS-CoV disease:** clinically compatible illness (i.e. early, mild-to-moderate, or severe) that is laboratory confirmed

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contacts have become ill. Epidemiologic evidence indicates that the transmission of SARS is facilitated by face-to-face contact, and this still appears to be the most common mode of spread in the form of droplet transmission. [1] However, airborne or fecal transmission may have a role in some settings, and it could account for the extensive spread within buildings and other confined areas that has been observed in some places in Asia. Transmission via casual contact is uncommon, but has been documented on an airplane or in a taxi. [1]

Peiris et al. [17] studied the viral load of SARS-CoV over time in respiratory secretions from 14 SARS patients and found the load in nasopharyngeal aspirates increased to a peak on the tenth day after onset of symptoms, then decreased gradually. Notwithstanding the small sample size and the effects of concomitant administration of
ribavirin and corticosteroid, this suggests that SARS patients might be most contagious in the second week of illness.

After the termination of the initial outbreak of SARS in July 2003, there were two further cases of SARS-CoV infection which were likely acquired in a laboratory setting, one case in late August and the other in December.\cite{18} This reinforces the necessity for careful laboratory practices when working with this virus. It appears there was no evidence of secondary transmission associated with either case, despite the active social activities undertaken by these two scientists after their exposure to SARS-CoV. An additional four community-acquired cases from the Guangdong Province of China were subsequently diagnosed from December 2003 through January 2004. Of interest, no close contacts of these cases was found to have fever or respiratory symptoms after home quarantine to date.\cite{19} More recently, in April 2004, the Chinese Ministry of Health reported additional cases of SARS which seemed to be initially associated with an index case of a 26-year-old female graduate student who worked at the National Institute of Virology in Beijing. The virus was apparently transmitted to the student’s mother and a nurse caring for the student (all three had might be most contagious in the second week of illness.

4. Clinical Manifestations

The initial descriptions of the clinical manifestations of SARS have come from reports of patients who have required hospitalization.\cite{8,21-24} In such patients the disease is often reported as a bi-phasic or tri-phasic illness with an initial acute febrile phase followed by a lower respiratory illness phase then progression in approximately 20–30% of patients to a phase characterized by acute respiratory distress syndrome (ARDS) necessitating ventilator support.

It is imperative to appreciate that individual patients do not necessarily display these ‘phases’, which could be highly individ-
Table II. Symptoms and abnormal laboratory test results of patients with severe acute respiratory syndrome (SARS) at presentation (%; based on the number of patients for whom the data were available)

| Symptoms          | Peiris et al. [17] (n = 50) | Lee et al. [23] (n = 138) | Poutanen et al. [22] (n = 10) | Tsang et al. [21] (n = 10) |
|-------------------|-----------------------------|---------------------------|-----------------------------|---------------------------|
| Fever             | 100                         | 100                       | 100                         | 100                       |
| Chills            | 74                          | 73                        | NR                          | 90                        |
| Cough             | 62                          | 57                        | 100                         | 80                        |
| Myalgia           | 54                          | 61                        | 20                          | 50                        |
| Rhinorrhea        | 24                          | 23                        | NR                          | 10                        |
| Diarrhea          | 10                          | 20                        | 50                          | 30                        |
| Headache          | 20                          | 56                        | 30                          | 70                        |
| Lymphopenia       | 68                          | 70                        | 89                          | 90                        |
| Thrombocytopenia  | 40                          | 45                        | 33                          | NR                        |
| Elevated CPK      | 26                          | 32                        | 56                          | NR                        |
| Elevated LDH      | NR                          | 80                        | 80                          | NR                        |
| Elevated transaminase | 34                | 23                        | 78                          | 70                        |

CPK = creatine phosphokinase; LDH = lactate dehydrogenase; NR = not reported.

ualized, from hyperacute to indolent presentation in time course. At the time of writing, the mortality of probable SARS cases was approximately 10%, but was much higher in older individuals and those with significant co-morbidities.

The mean incubation period of SARS is estimated to be 6 days, with a usual range up to approximately 10 days after exposure. [1,2,15,25] The illness generally begins with a prodrome of fever, often associated with chills, rigors and myalgia. Headache and severe malaise may accompany this phase; rash has been absent in most cases. In one outbreak within an apartment complex in Hong Kong, diarrhea was found in 66% of cases. [1] After a typical period of 3–7 days, a lower respiratory phase may begin with the onset of non-productive cough and progressive pneumonia. In the initial reports of cases, 20–30% of patients required intensive care unit management and mechanical ventilation. The presenting symptoms of patients admitted to the hospital from four published series are listed in table II. [8,21-23] Most patients were admitted to the hospital several days after the onset of symptoms. The most common complaints were fever and chills or rigors. Upper respiratory tract symptoms such as rhinorrhea and sore throat were less common. At the time of examination, abnormal auscultatory findings were present in about one-third of patients.

Although fever and progressive respiratory manifestations are a hallmark of most cases of SARS, patients with more indolent characteristics (including absence of fever) have been described – especially in elderly or immunocompromised patients. [1,26]

The first report of a complete outbreak of SARS (from beginning of the outbreak until declaration of containment) was recently published by Vu et al. [27] They report a cohort of patients, all of whom required hospitalization, who presented with similar manifestations as the patients described above (figure 2). Although the majority of patients developed symptoms of respiratory tract infection during admission, only a minority of patients had symptoms at the time of admission to the hospital. Diarrhea was present in only 10% at the time of admission, but 50% developed this symptom while in the hospital. These investigators also observed the duration of time from the onset of illness until the evolution of various endpoints of their disease: fever, 0.3 days; admission to the hospital, 4 days; oxygen therapy, 4 days; mechanical ventilation, 6 days; and death, 18 days.

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hospital, 4.3 days; onset of radiographic change, 4.4 days; onset of respiratory symptoms, 4.5 days; onset to maximal radiographic change, 10 days; onset to intubation, 10.5 days; onset to end of fever, 12.7 days; and onset to death, 18.8 days.[27]

Chest x-ray abnormalities are usually absent during the initial phase of illness but become progressively abnormal during the phase of lower respiratory illness. Initially this is characterized by early focal interstitial infiltrates, usually seen as ground glass opacity, and progressing to bilateral disease (figure 3). A typical ARDS picture has emerged in many very seriously ill patients. In these patients, high-resolution computed tomography (HRCT) is more sensitive in early disease when the chest x-ray could be normal or only showing inconclusive consolidation. Characteristically, HRCT shows peripheral and, most commonly, lower lobe consolidation.[28,29] Although non-diagnostic and closely mimicking the appearance of bronchiolitis obliterans with organizing pneumonia, HRCT is also helpful for showing no evidence of pleural effusion or intrathoracic lymphadenopathy, which are very rarely seen in SARS.[2,21,28,29] Spontaneous pneumomediastinum also occurs as a rare complication with SARS.[8]

Laboratory abnormalities most often associated with SARS include absolute lymphopenia, mild neutropenia, and thrombocytopenia. Mild to moderately elevated plasma levels of creatine phosphokinase, lactate dehydrogenase, and transaminases were seen in 30–80% of cases (table II).

Lee et al.[23] found that advanced age, male sex, and high levels of serum creatine phosphokinase, serum lactate dehydrogenase, a relatively high initial neutrophil count (i.e. mean 4.6 vs 3.7 × 10^9/L), and a low levels of serum sodium were significant predictive factors for intensive care unit admission, and death. On multivariate analysis, the only factors that were predictive of an adverse outcome were advanced age, a high peak lactate dehydrogenase level, and a higher absolute neutrophil count.

5. Diagnosis

The initial manifestations of SARS are not specific and cannot easily be distinguished from those of other respiratory infections. The first clinical definition developed by the WHO (see section 1) was found to be only 29% sensitive and approximately 70% specific for identifying laboratory documented cases.[30] Clinicians should conduct thorough diagnostic testing to rule out other etiologies in patients suspected of having SARS. Initial recommended diagnostic testing procedures include chest radiograph and pulse oximetry. Since SARS often progresses rapidly, repeated chest x-rays within the first or second day, sometimes twice daily, may be helpful in documenting the course of disease. Indiscriminate use of HRCT to detect ‘radiographically occult disease’ is to be discouraged in view of infection control issues, and the rapidly progressive nature of SARS, thus making it likely that radiographic abnormalities would be more apparent within a few days after hospitalization.[2] Tests for evaluation of specific organisms associated with pneumonia should be performed, and include: blood cultures, sputum Gram stain and culture, and testing for viral respiratory pathogens – especially influenza and respiratory syncytial virus. Urinary antigen for both *Pneumococcus* spp. and *Legionella* spp. should also be considered. Acute and convalescent serum (preferably 28 days after onset of symptoms) should be collected from each patient who meets the SARS clinical case definition. However, if acute and convalescent phase sera are collected at least 8–10 days apart, a 4-fold or greater rise in

![Fig. 3. Serial chest x-ray findings in a 28-year-old woman with severe acute respiratory syndrome. The patient presented acutely 3 days after onset of a high fever, and was immediately hospitalized upon attendance at the Accident and Emergency Department.](image)
different RT-PCR assays performed on different specimen aliquots identify the coronavirus RNA. Because of the possibility of false-negative cultures and RT-PCR assays, only the absence of antibody in a serum specimen obtained >21 days after symptom onset is considered by the CDC to be a negative laboratory test for SARS coronavirus.

The likelihood of detecting SARS-CoV is increased if multiple specimens (e.g. stool, serum, respiratory tract specimens) are collected during the course of illness. Clinicians should consult with their local laboratory personnel and health department about obtaining such tests. The priority of specimens for SARS-CoV testing and optimal timing for collection are presented in table III.

Of the 50 patients with clinical SARS described by Peiris et al., 45 had serological or PCR evidence of SARS-associated coronavirus infection; and of the 5 who were unconfirmed, 4 had serological testing prior to 14 days of onset of illness (possibly prior to the time of seroconversion). Another series of 72 cases in Hong Kong showed that despite significantly high dosages of corticosteroid therapy, a seroconversion of 95.8% occurred on day 21 after onset of illness. This differs from the US experience where of the 74 probable cases of SARS reported by 15 July 2003, only 8 had been confirmed by laboratory diagnosis (all by serology); 38 were negative and 28 had no result.

Table III. A summary of specimens recommended for testing for severe acute respiratory syndrome-associated coronavirus[34]

| Specimen type       | <1 week after symptom onset | 1–3 weeks after symptom onset | >3 weeks after symptom onset |
|---------------------|-----------------------------|-------------------------------|-----------------------------|
| RT-PCR              |                             |                               |                             |
| Sputum              | x                           | xx                            | x                           |
| BAL, pleural fluid  | x                           | xx                            | x                           |
| NP wash/aspirate    | x                           | xx                            | x                           |
| NP/oropharyngeal swab| x                           | xx                            | x                           |
| Serum/plasma        | xx                          | x                             | Not recommended             |
| Stool               | x                           | xx                            | xx                          |
| EIA                 | xx                          | xx                            | xx                          |

a It is recommended that clinicians obtain signed informed consent prior to testing.
b Antibody testing should also be carried out on a serum sample collected >28 days after symptom onset.

BAL = bronchoalveolar lavage; EIA = enzyme immunoassay; NP = nasopharyngeal; RT-PCR = reverse transcription-polymerase chain reaction; x indicates level of virus detection.

antibody titer when tested in parallel should be considered indicative of a confirmed case.

A variety of methods for detection of coronavirus infection are now available. These include culture methods, PCR-based methods, and serological tests.[31]

Culture of the SARS coronavirus is considered solid evidence of infection, but there have been problems with the various generations of RT-PCR assays, both with false-positive results and with inconsistent detection of viral genome in the first days of illness as well as later in the convalescent phase. It is therefore recommended that detection of SARS-CoV RNA by RT-PCR be validated by a second reference laboratory.[32] Because antibodies to SARS coronavirus have not been found in the general population, background SARS coronavirus antibodies do not appear to be a substantial concern. However, the current serologic assays (both ELISA and IFA [indirect fluorescent antibody] formats) do not reliably detect antibodies until the titers rise substantially after the second week of illness. According to the USCDC, suspect or probable cases are considered laboratory-confirmed if SARS coronavirus is isolated, if antibody to SARS coronavirus is detected and confirmed by a second reference laboratory, or if two different RT-PCR assays performed on different specimen aliquots identify the coronavirus RNA. Because of the possibility of false-negative cultures and RT-PCR assays, only the absence of antibody in a serum specimen obtained >21 days after symptom onset is considered by the CDC to be a negative laboratory test for SARS coronavirus.

The likelihood of detecting SARS-CoV is increased if multiple specimens (e.g. stool, serum, respiratory tract specimens) are collected during the course of illness. Clinicians should consult with their local laboratory personnel and health department about obtaining such tests. The priority of specimens for SARS-CoV testing and optimal timing for collection are presented in table III.

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Table IV. A summary of infection control precautions for patients hospitalized with suspected/probable severe acute respiratory syndrome (SARS) [reproduced from Sampathkumar et al.,[39] with permission]

| Precaution                                                                 |
|---------------------------------------------------------------------------|
| Place patient in a negative pressure, specially vented, room              |
| Maintain a log of everyone entering the patient’s room                    |
| Restrict visitors as much as possible                                     |
| Limit the number of hospital personnel caring for the patient            |
| All healthcare workers entering the room should use a combination of      |
| contact (gowns, gloves, hand hygiene) and airborne (N-95 respirator)      |
| precautions and eye protection                                            |
| Minimize air turbulence when changing linen                               |
| Limit cough-inducing procedures (sputum induction, administration of      |
| nebulized medications, suctioning, bronchoscopy)                         |
| Avoid use of noninvasive positive pressure ventilation (e.g. CPAP,       |
| BiPAP)                                                                   |
| For patients receiving mechanical ventilation, use closed-suctioning      |
| devices, HEPA filtration on exhalation valve port                         |
| Educate personnel involved in the care of these patients to be vigilant  |
| for symptoms of SARS for 10 days after contact with the patient           |
| Quarantine personnel who have had unprotected contact with a SARS patient|
| during an aerosol-generating procedure                                     |

BIPAP = biphasic positive airway pressure; CPAP = continuous positive airway pressure; HEPA = high-efficiency particulate air.
Table V. A summary of protective measures taken by severe acute respiratory syndrome (SARS)-infected and non-infected staff in Hong Kong hospitals (reproduced from Seto et al.,[40] with permission from Elsevier)

| Protective measures\(a\)                  | Infected staff \((n = 13)\) | Non-infected staff \((n = 241)\) | Two-tailed \(p\)-value |
|---------------------------------------------|------------------------------|----------------------------------|------------------------|
| Masks\(b\)                                 | 2 (15%)                      | 169 (70%)                       | 0.0001                 |
| paper mask                                 | 2                            | 26                              | 0.511\(^c\)           |
| surgical mask                              | 0                            | 51                              | 0.007\(^c\)           |
| N-95                                       | 0                            | 92                              | 0.0004\(^c\)          |
| Gloves                                     | 4 (31%)                      | 117 (48%)                      | 0.364                  |
| Gowns                                      | 0 (0%)                       | 83 (34%)                       | 0.006                  |
| Hand-washing                               | 10 (77%)                     | 227                             | 0.047                  |
| All measures                               | 0 (0%)                       | 69 (29%)                       | 0.022                  |

\(a\) 'Yes' and 'most of the time' were grouped together.

\(b\) Total cases 254 by forward (Waldesian) logistic regression.

\(c\) Comparing proportion of infected \((n = 11)\) over non-infected staff \((n = 72)\), with those without mask.

6. Treatment

At the time of writing (24 May 2004), no specific therapy is recommended. A variety of treatments have been attempted, but there are no controlled data. Most patients have been treated throughout the illness with broad-spectrum antimicrobials, supplemental oxygen, intravenous fluids, and other supportive measures.

Some clinicians have advocated a combination of ribavirin and corticosteroids, but the efficacy of these drugs has not been established. The use of systemic corticosteroids in SARS is controversial, and the efficacy based on controlled studies is unavailable.[36] One study found initial use of pulse-dosed methyl prednisolone (≥500 mg/day) to be more efficacious and equally well tolerated as a lower dose of methyl prednisolone, but this was based on retrospective observational evaluation.[35] The use of corticosteroids in patients with viral infections can be hazardous when not accompanied by an effective anti-viral agent.[36] Early testing of ribavirin and other antiviral compounds against the novel coronavirus have not produced evidence of in vitro activity.[31] An evaluation of the use of ribavirin was published by Knowles et al.,[37] who reported adverse events in 110 patients with suspected or probable SARS treated with ribavirin. Of those 110 patients 61% had evidence of hemolytic anemia; hypocalcemia and hypomagnesemia were detected in 58% and 46% of patients, respectively.[33] The authors felt the benefits of ribavirin may not outweigh the risk of adverse events. There was a potential for ribavirin to have negative clinical and economic consequences because of the adverse events. It is now considered among the Hong Kong pulmonologists that ribavirin alone is not indicated as antiviral therapy against SARS-CoV.

A number of other agents have been suggested for therapy of SARS-CoV, including interferon-α, glycyrrhizin, and protease inhibitors.[1] In one preliminary, uncontrolled study by Loutfy et al.[38] from Toronto, use of interferon 9 μg/day for a minimum of 2 days and increased to 15 μg/day for a total of 10 days, plus corticosteroids (oral prednisone 50mg twice a day, or intravenous methylprednisolone 40mg every 12 hours) was associated with reduced disease-associated impaired oxygen saturation and more rapid resolution of radiographic lung abnormalities. The authors acknowledge, however, that these findings need to be interpreted cautiously in view of lack of randomization, the retrospective dosing, and the limited sample size (a total of 21 patients).

7. Prevention

Since the causative agent of SARS is contagious, in the absence of effective drugs or vaccines the only currently effective strategy for limiting the impact of SARS is implementation of preventive
Radiographic evidence of pneumonia or ARDS of unknown etiology requiring hospitalization

Yes

Continue droplet precautions and treat as indicated in Infectious Diseases Society of American guidelines for community-acquired pneumonia

The clinician should ask the patient about the following:

- Recent travel (within 10 days) to mainland China, Hong Kong, or Taiwan (or other countries thought to be at higher risk) or close contact with ill persons with a history of travel to such areas
- Employment in an occupation at particular risk for SARS-CoV exposure, including a healthcare worker with direct patient contact or a worker in a laboratory which contains live SARS-CoV
- Close contact with others who have been told they have pneumonia

If no evidence, treat as clinically indicated

Yes to one of three questions

1 Notify the health department
2 Evaluate for alternative diagnosis as clinically indicated. This work may include the following:
   - Complete blood count with differential
   - Pulse oximetry
   - Blood cultures
   - Sputum Gram stain and culture
   - Testing for viral respiratory pathogens such as influenza A and B, respiratory syncytial virus
   - Specimens for legionella and pneumococcal urinary antigen
3 The health department and clinicians should look for evidence of clustering of patients with radiographically confirmed pneumonia without alternative diagnosis (e.g. while travelling, exposure to other cases of pneumonia, clusters of pneumonia among healthcare workers)
4 NOTE: If the health department and clinician have a high suspicion for SARS-CoV infection, consider SARS isolation precautions (http://www.cdc.gov/ncidod/sars/ic.htm) and immediate initiation of the algorithm in this figure

Yes

After 72h, alternative diagnosis?

Yes

Treat as clinically indicated

No

If part of a cluster of pneumonia (or there are other reasons to consider at higher risk for SARS-CoV disease), consider SARS-CoV testing in consultation with health department

Continue treating pneumonia as clinically indicated

Fig. 4. Algorithm for evaluating and managing patients requiring hospitalization for radiographically confirmed pneumonia, in the absence of person-to-person transmission of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) anywhere in the world. [34]
An important characteristic of the recent SARS outbreaks has been the predilection for transmission to healthcare providers after patient care. For the most part this has occurred after close, unprotected contact with symptomatic individuals. Healthcare workers who have had unprotected exposure and who develop fever or respiratory symptoms should not come to work, and should report their symptoms to the infection control/employee health service and their physician immediately. Healthcare workers who have had unprotected exposure during procedures with high risk of aerosolization (e.g. intubations, bronchoscopy) should be quarantined for a 10-day period, since there is a high risk of infection transmission. Table IV lists precautions for patients hospitalized with SARS.

Patients with SARS-CoV disease who do not otherwise need to be hospitalized can be managed appropriately as outpatients. These patients should limit interactions outside the home. They should be instructed to wear surgical masks in the presence of household contacts, contain respiratory secretions in facial tissues, and wash hands frequently. They should stay away from work, school, or other public places for 10 days after resolution of fever. Household members or other close contacts of these patients should wear gloves and practice good hand hygiene. In the ab-
The importance of SARS precautions was demonstrated in a case-control study in five Hong Kong hospitals, with 241 non-infected and 13 infected healthcare providers who had documented contacts with SARS patients (table V). All of the healthcare providers were surveyed concerning the use of masks, gloves, gowns, and hand-washing, as recommended under droplet precautions. No staff member who reported use of all four measures was infected. In contrast, all 13 infected staff members had omitted at least one of the measures \( p = 0.0224 \). The authors observed that both surgical and high efficiency masks (N-95 masks) were protective against infection, whereas paper masks did not significantly reduce the transmission (such masks are easily wet with saliva and are not recommended for precautions against droplets).

In order to be prepared for the recurrence of SARS and the need for early implementation of control measures, the US CDC released clinical guidelines for the identification and evaluation of possible SARS-CoV disease among patients presenting with community-acquired illness. The key principles upon which control measures are based have taken into consideration the fact that in the year 2003 a vast majority of patients with SARS-CoV disease had a clear history of exposure either to a SARS patient or to a setting in which SARS-CoV transmission occurred (i.e. hospital); and developed pneumonia. Recommendations for the evaluation of patients with community-acquired respiratory illness were developed for two primary circumstances: firstly in the absence of SARS-CoV transmission anywhere in the world, and secondly once transmission had been documented (these were released prior to the reports of recent cases in the Guandong province of China) [table VI, figure 4, and figure 5]. In the light of reports of SARS from China in late December 2003 and January 2004, the CDC recommended that US physicians maintain a greater index of suspicion of SARS in patients who required hospitalization for radiographically confirmed pneumonia or acute respiratory distress syndrome and who had a history of travel to the Guandong Province in China (or close contact with an ill person with a history of recent travel to the area) in the 10 days before onset of symptoms. When such patients are identified, appropriate isolation precautions (contact and airborne) for SARS should be taken immediately and the suspected patient should be tested for evidence of SARS-CoV infection as part of the diagnostic evaluation.

Since Hong Kong is considered a potential area at relatively high risk for recurrence of SARS, infection control measures in that country continue to be at a high level of alert. In Hong Kong, the vast majority of patients with fever \( \geq 38^\circ \text{C} \) and community-acquired pneumonia are admitted to isolation wards to exclude SARS. This policy has been running since the middle of March 2003 at Queen Mary Hospital of the University of Hong Kong, despite the disappearance of SARS in Hong Kong since June 2003. Only authorized and minimum number of staff working in these wards may enter the premises. All staff entering these restricted areas follow strict and stepwise ‘gowning’ and ‘degowning’ procedures, and use standard personal protection equipment (disposable surgical paper cap, N-95 mask, and reusable eye goggles and cotton surgical gown). Patients are treated with potent antibiotics, usually in the form of a combination of cephalosporin and macrolide, or in the event of allergy to these antibiotics with levofloxacin. Patients who improve clinically and radiologically are unlikely to have SARS, and are moved to wards that don’t require the level of intensive care and/or isolation as would be required for those patients who have SARS, for observation for 5–7 days before discharge. In the event of confirmed or suspected SARS, a patient will be diverted to the appropriate wards to minimize exposure of fellow patients, if no single-room accommodation could be provided.

8. Conclusion

Because a new virus causes SARS, it is very difficult to predict the eventual significance of this infection. However, the re-emergence of sporadic cases in China, has caused great concern as to its future impact. It has had enormous economic and political impact on the affected areas of the world. Although important progress has been made concerning the etiology, epidemiology, and prevention of this virus, many important questions remain.

- Why do some people develop severe illness and others have only mild symptoms?
- Is there a large segment of infected patients with subclinical infection?
- Will there be specific antiviral therapy?
- Will a vaccine be effective?
- Most importantly, to what extent will SARS re-emerge?

Without answers to some of these questions, the eventual outcome of SARS remains unclear.

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