Severe Acute Respiratory Syndrome (SARS) Coronavirus

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ABSTRACT

The global severe acute respiratory syndrome (SARS) outbreak was the first pandemic of the 21st century. Although the outbreak was successfully controlled, evidence that SARS emerged from an animal reservoir has raised concerns that another pandemic could occur. This review discusses the likelihood of another SARS pandemic and reviews the epidemiological and clinical features of the disease with an emphasis on the clinical presentation, diagnosis, and management of SARS.

KEYWORDS: SARS, pandemic, coronavirus

The global SARS outbreak was the first pandemic of the 21st century: in less than a year, cases were identified in 26 countries.[1] Local, national, and international efforts at outbreak control were successful, and the outbreak was declared over on July 5, 2003, 8 months after SARS appeared in southern China and 5 months after initial international spread. Currently, we are in an "interepidemic period", with no ongoing transmission of SARS occurring in humans.

This article summarizes the current state of knowledge on the epidemiology, clinical presentation, diagnosis, treatment, and prevention of SARS by addressing five fundamental questions: What is the likelihood of another global SARS outbreak? When should SARS be suspected in a patient with an unexplained febrile respiratory illness? How can the diagnosis be confirmed? How should patients with suspected or confirmed SARS be managed? How can in-hospital transmission of SARS be prevented?

THE GLOBAL SARS OUTBREAK

SARS emerged in the Guangdong Province of southern China, with the first reported case developing illness on November 16, 2002. Between November and February, clusters of cases of an unexplained "atypical" pneumonia occurred in several regions of Guangdong.[2–4] On January 31, 2003, a patient with an unexplained atypical pneumonia was admitted to the second affiliated hospital of Zhongshan University in Guangdong. This patient triggered a large, hospital-wide outbreak, and the direct transmission to 59 health care workers and 19 family members resulted in rapid amplification of the scope of the outbreak in the region.[3,4] China reported the outbreak to the World Health Organization (WHO) on February 11, by which time cases had been recognized in seven provincial municipalities, 305 cases had occurred, and five patients had died.[4]

On February 21, a nephrologist involved in the care of patients with the atypical pneumonia syndrome at the second affiliated hospital of Zhongshan traveled to Hong Kong to attend a wedding and stayed at the Metropole Hotel. He was symptomatic on arrival at the hotel and transmitted SARS to 16 hotel guests and visitors before requiring hospitalization less than 24 hours later, on February 22.[3,5] The infected guests included international travelers; the return of these travelers to their countries of origin resulted in the

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SARS outbreaks seen in Vietnam, Canada, Singapore, and the Philippines as well as isolated cases in Ireland and the United States.[4] Admission of guests and hotel visitors to local hospitals also precipitated the Hong Kong SARS outbreak. On March 12, the World Health Organization (WHO) released its first global alert describing nosocomial outbreaks in Vietnam and Hong Kong, and the larger outbreak in Guangdong.[6] Following the release of the alert, cases were reported to the WHO from Canada, Indonesia, the Philippines, Singapore, and Thailand. On March 15, the WHO released a second alert that coined the term *severe acute respiratory syndrome (SARS)* and included a travel advisory.[7]

By the end of March, a cooperative international scientific effort had identified the etiologic agent of SARS as a novel human coronavirus (SARS-CoV).[8–10] Testing in nonhuman primates confirmed that SARS-CoV was both necessary and sufficient to reproduce a SARS-like illness, fulfilling Koch's postulates.[11,12] The WHO confirmed that SARS-CoV was the etiologic agent of SARS on April 16, 2003. Simultaneously, countries grappling with SARS used traditional epidemiological methods to control the spread of SARS. Without a diagnostic test, a case definition was developed, cases were identified and isolated, contact tracing was initiated, contacts were quarantined, and in-hospital infection control strategies designed to limit the spread of SARS were implemented. As a result of these efforts, the chain of human transmission of SARS was officially terminated on July 5, 2003. Human infections with animal SARS-like coronaviruses have subsequently been reported; however, there have been no further cases of disease due to the human virus, SARS-CoV.

Although the effort to control SARS was successful, the consequences of the SARS pandemic were substantial, with 8096 cases and 774 fatalities reported from 26 countries, yielding a case fatality rate of 9.6%.[1] The economic impact of SARS was estimated to have been between US$30 and 140 billion.

ORIGINS OF THE HUMAN SARS CORONAVIRUS

Understanding the origins of SARS-CoV is the crucial step in evaluating the likelihood of the reemergence of SARS. The recognition that people working in the food industry or in the wet markets of Guangdong were overrepresented among the earliest cases of SARS led to the suspicion that SARS was a zoonotic disease.[13] Testing of the animals in the wet markets identified infection with a SARS-like coronavirus in several mammalian species, including Himalayan palm civets, Chinese ferret badgers, and raccoon dogs.[14] Over 80% of civet cats were positive for SARS in some animal markets.[15,16] Although SARS-CoV was not closely related to other known human or animal coronaviruses, there was over 99.8% homology between SARS-CoV and the SARS-like coronavirus found in the animal markets.[14,17,18] Serological studies subsequently demonstrated that 13% of animal traders in Guangdong had antibody to SARS-CoV as compared with only 1 to 3% of market and community controls.[19] These data suggest that SARS is a zoonosis that entered the human population via contact with Himalayan palm civets or other exotic mammals in the wet markets of Guangdong.

Although SARS likely passed from civet to human, it appears that the palm civet is not the natural reservoir of SARS-like virus from which SARS-CoV evolved. Testing at the farms that supply civets to the markets did not identify seropositive civets, suggesting that infection occurred after their arrival at the marketplace.[15,16] Furthermore, the viral genome is not at equilibrium in either the human or the civet host, suggesting that neither is the original reservoir of the virus.[16,18] Surveys of wild animals in China have identified infection with SARS-CoV like viruses in three species of bat, but not in Himalayan palm civets, Chinese ferret badgers, or other mammalian, reptilian, or avian species.[20,21] The virus appears to be well adapted to the bat host because it is genetically diverse and does not appear to cause clinical disease.[20,21] Thus, bats may be the natural reservoir from which SARS-CoV evolved.

WILL ANOTHER PANDEMIC OCCUR?

After the SARS pandemic ended some experts predicted annual winter outbreaks, whereas others felt that a recurrence of a SARS pandemic was highly unlikely.[22] Although yearly outbreaks have not materialized, SARS has reentered the human population on three occasions, and SARS-like disease from related animal SARS-like coronaviruses has also occurred.

Laboratory accidents in Singapore, Taiwan, and China have resulted in four laboratory workers contracting SARS; in the Chinese laboratory, infections in two laboratory workers resulted in transmission to seven others.[23–25] Following the removal of a ban on the sale of exotic animals in southern China, SARS-like viruses were again noted to be prevalent among civet cats in the wet markets, and four human cases of SARS-like disease were reported in rapid succession, the first in December 2003, 4 months after the ban was lifted.[13,16,18,26,27] All four cases had potential contact with exotic animals, there was no evidence of human-to-human transmission, and the viruses isolated were more similar to the civet cat viruses than human SARS-CoV from the 2003 pandemic. Infection of humans with SARS-CoV-like viruses also appears to have occurred prior to the global SARS outbreak because 1.8% of 938 serological specimens from Hong Kong residents stored in 2001 demonstrated detectable antibodies to a SARS-like coronavirus.[28]

Although efforts are being made to ensure that additional laboratory accidents involving SARS-CoV do not occur, the potential for the reemergence of SARS from an animal reservoir remains. The marketing and consumption of wild animals, including civet cats, continues in China despite the reimposition of laws banning their sale.[13] Thus it appears certain that humans in southern China will continue to be exposed to SARS-like coronavirus and will continue to develop infection as a result. The ability of SARS-CoV to transmit efficiently from person to person is due to the specificity of the SARS-CoV spike protein, which selectively binds the human angiotensin-converting enzyme 2 receptor (ACE2).[29] It is possible that the mutational changes that occurred in the spike protein of a SARS-like virus to create a human virus was a unique event, and will not be repeated. However, it is also possible that selective pressure within exotic animal markets will lead to this type of mutation repeatedly, and that future outbreaks of SARS CoV will occur.[30]

Given the presence of a natural reservoir of SARS-CoV like virus and the evidence that such viruses have persistently affected the human population, it appears likely that isolated cases, and possibly small outbreaks of SARS-like illnesses, will continue to occur. Despite this, another pandemic is unlikely to occur for several reasons. The recognition that SARS emerged from an animal reservoir in southern China and the development of serological tests for SARS make it possible to conduct surveillance of human and animal populations in this region. It is therefore likely that future outbreaks would be detected at a much earlier stage. The clinical features of disease and the availability of laboratory testing mean that cases can be identified and appropriately managed much more easily. In addition, public health and hospital infection control strategies capable of controlling the spread of SARS are now well understood and not difficult to implement. In this context, it is reassuring that the three laboratory accidents resulting in human SARS infections were successfully detected and contained with no or few secondary cases.

Despite this, it is important to remain cautious and vigilant. The events at the Metropole Hotel demonstrate that a single highly contagious case in an international traveler or an individual who frequents a train station, airport, hotel, or any large gathering of travelers could rapidly trigger another pandemic. If cases are disseminated to countries that did not experience the first SARS outbreak or that lack the public health infrastructure to detect and manage SARS, another large outbreak could result. One of the recent Chinese cases traveled by train from Anhui to Beijing and back to Anhui, while symptomatic.[25] Had she been in the highly contagious phase of SARS, a large outbreak might have occurred. Thus ongoing surveillance and awareness of SARS are critical in minimizing the likelihood of another pandemic, and the possibility of future outbreaks remains a real concern. It is our responsibility to learn from our experience with SARS and, as front-line clinicians, to be familiar with the epidemiology and clinical presentation of SARS. Rapid identification of the next case of SARS is the critical step in preventing an outbreak.

THE EPIDEMIOLOGY OF SARS

Incubation Period

The incubation period of SARS ranges from 2 to 14 days, with a mean incubation period of 4 to 6 days.[3] The upper 95th percentile of the incubation period ranges from 9.5 days to 13.9 days, depending on the cohort studied and the methodology used to estimate incubation.[31] This is longer than the 10-day upper limit used in case definitions of SARS and in defining the appropriate quarantine period for SARS contacts. SARS should not be excluded as a diagnosis based solely on an incubation period > 10 days.

Period of Infectivity

SARS is unlike the majority of other viral illnesses in that the period of maximum infectivity does not occur at or before the time of symptom onset. Instead, the period of maximum infectivity occurs in the second week of illness and at the time of rapid clinical deterioration.[3,32] This correlates with the peak viral load observed in respiratory secretions.[3,32] Transmission from patients prior to the onset of symptoms or 10 days after the resolution of fever has not been observed.[3,32] SARS transmission is also uncommon in patients who are recognized to have SARS and for whom droplet/contact precautions are initiated within 5 days of symptom onset.[3]

SARS was to a large extent nosocomially transmitted. The proportion of cases resulting from nosocomial spread to healthcare workers ranged from 19% in mainland China to 57% in Vietnam.[33] The tendency of cases to be maximally infective during the second week of illness, by which time the vast majority of cases were already hospitalized, is likely the key reason for the degree of nosocomial transmission reported. Additionally, the most contagious patients are also the patients most likely to require intensive care, intubation, and other procedures requiring close contact with the airway, all of which were clearly associated with increased transmission of SARS in hospitals.[34–37]

Mode of Transmission

SARS appears to be transmitted primarily by the droplet and contact routes. This conclusion is based both on the

pattern of transmission seen in the initial SARS outbreaks and the effectiveness of infection control measures geared to interrupt such transmission, including the use of surgical masks, gowns, gloves, eye protection, and hand hygiene.[3,37–42] However, some evidence suggests that airborne transmission may occasionally occur. In the Amoy Gardens outbreak, aerosolization of infected feces into the building airshaft appeared to result in widespread airborne transmission.[43] Transmission to health care workers performing procedures involving the airway also resulted in transmission despite the use of contact and droplet precautions, suggesting either such high infectivity that minor breaks in technique resulted in transmission, or that aerosolization and limited airborne transmission may have occurred.[44–46]

THE CLINICAL PRESENTATION, CLINICAL COURSE, AND PROGNOSIS OF SARS

The clinical presentation of SARS is dependent on the duration of illness at the time of assessment.[13,32,47,48] During the first few days of the illness, a prodromal phase occurs that is characterized by fever, chills, myalgia, malaise, and headache.[13,32,48] Some patient also have diarrhea.[38,39] Symptomatic fever was reported in greater than 99% of patients in most series; the incidence of other symptoms has varied widely in different reports.

Respiratory symptoms are typically absent, although a mild, nonproductive cough may occur. Physical examination is often unremarkable early in disease and the findings on pulmonary auscultation are less than would be expected based on the chest radiograph; fewer than one third of patients have crackles.[32] Furthermore, 40 to 50% of patients may have normal chest radiography at initial presentation, particularly if the patients are first seen less than a week after the onset of illness.[32,47] Ground-glass opacities may be detected on chest computed tomography (CT) before abnormalities are apparent on the chest x-ray.[49–53] Lymphopenia, thrombocytopenia, and elevations of lactate dehydrogenase (LDH), creatine kinase (CK), and alanine aminotransferase (ALT) are seen early in some patients.[47]

Most patients then enter a respiratory phase that begins late in the first week or early in the second week of illness.[13,47,48] Fever may improve or resolve at this stage while respiratory symptoms (i.e., nonproductive cough, dyspnea) develop and/or worsen. Diarrhea commonly develops at this point and may occur in up to 70% of patients.[54] Pulmonary infiltrates are now present in most patients. Early findings include ground-glass opacities, followed by the development of focal and unilateral consolidation that is typically peripheral with a lower lung predominance.[55] Progression to multifocal and then bilateral consolidation occurs in most cases.[55,56] Progressive lymphopenia, thrombocytopenia, and elevations of LDH, CK, and ALT may be observed.[47] Some patients develop hypoxemia.

Most patients begin to recover late in the second week or early in the third week of illness, with gradual improvement in respiratory symptoms, stabilization, and gradual improvement in the radiographic appearance and normalization of the lymphocyte count and other hematological and biochemical markers.[32,48] Most patients make a complete recovery, although the psychological impact of SARS should not be underestimated.

Although most patients make a full recovery from SARS following the respiratory phase, approximately 20 to 30% of patients develop worsening disease with progressive respiratory failure. At this point the radiographic appearance typically evolves to diffuse consolidation indistinguishable from acute respiratory distress syndrome (ARDS).[55,56] The median time from disease onset to mechanical ventilation among patients that developed respiratory failure due to SARS was 9 days (IQR [interquartile range] 7 to 13 days) (M. Muller, unpublished data). The mortality in this subset was substantial, approaching 50%.[57,58]

Atypical presentations of SARS were reported throughout the outbreak and often contributed to transmission of SARS due to late diagnosis. Asymptomatic SARS in adults was rare but did occur occasionally.[3,59–61] Mild cases with prodromal symptoms but without respiratory symptoms or pulmonary infiltrates and occasional cases characterized by fever and diarrhea without respiratory symptoms were reported.[48,62] Although fever was the cardinal symptom of SARS, occurring in $>97\%$ of cases, some patients had fever resolve prior to presentation, and in a small number of cases no fever was ever documented. This occurred most frequently in elderly patients with comorbidities.[38,47,63] SARS was uncommon in children and appeared to be a milder illness in children than in adults.[64–66] In teenagers, the presentation was similar but milder than in adults, whereas in younger children presentation was often with fever and rhinorrhea, an unusual finding in adults.[66]

The overall global case fatality rate with SARS was 9.6%, but ranged from 7 or 8% in China and Vietnam to 17% in Canada and Hong Kong.[33,38,39,57,58] The reason why some patients recover spontaneously whereas others develop progressive respiratory failure has not been explained; despite this, numerous prognostic factors predictive of severe disease have been identified. The most consistently identified prognostic factors identified in multivariate analysis from multiple studies include age, comorbidity (especially diabetes mellitus and cardiac disease), elevation of LDH and absolute neutrophil count (ANC) at diagnosis, thrombocytopenia, hypoxemia, and extent of radiographic involvement.[38,39,54,58,67–84]

THE DIAGNOSIS OF SARS

The diagnosis of SARS was one of the great challenges of the global SARS pandemic. Prior to the identification of the etiological agent and the development of specific microbiological tests, the diagnosis was based entirely on clinical and epidemiological considerations. Although the testing for SARS has improved dramatically, clinical diagnosis is still required to identify patients that require testing for SARS and to guide initial management because there are no sensitive and specific microbiological tests that give consistent and reliable results in the first 4 days of illness.

The Clinical and Epidemiological Diagnosis of SARS

The presenting symptoms and signs of SARS are nonspecific. Early SARS resembles a variety of febrile infectious diseases, including influenza, whereas the respiratory phases of SARS are consistent with other causes of community-acquired pneumonia. Furthermore, the chest x-ray and CT abnormalities seen reflect air space disease that cannot be distinguished from other causes of pneumonia, and the hematological and biochemical findings also occur frequently with other etiologies of pneumonia.[55,56,85]

The initial case definitions of SARS are shown in Table 1. The diagnostic accuracy of the WHO definitions has been examined in both high- and low-prevalence settings.[61,86–88] The positive predictive value ranged from 96% in a specialized SARS clinic in Hong Kong, to 11% in a general hospital in Singapore, to 4% in the United States. As the prevalence of disease decreased, the likelihood of false-positive findings rose. The poor positive predictive value of the case definition in the United States may also be due to the fact that direct exposure to SARS cases is a much stronger predictor of SARS than indirect exposures such as travel to a particular city where disease may be occurring, and direct exposure is more common in areas experiencing large outbreaks (e.g., Hong Kong, Singapore), whereas travel-related exposure is more common in other areas (e.g., the United States).[47]

Despite the nonspecific nature of the illness and the limitations of the case definitions used, there are clinical and epidemiological clues that can raise the suspicion of SARS sufficiently to require additional testing and isolation and others that can lower the suspicions of SARS. During the epidemic period, exposure status is

Table 1 World Health Organization Clinical, Epidemiological, and Laboratory Definition of Severe Acute Respiratory Syndrome

Clinical Evidence for SARS
1. A history of fever, or documented fever $\geq$38°C (100.4°F)
AND
2. One or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath
AND
3. Radiographic evidence of lung infiltrates consistent with pneumonia or ARDS or autopsy findings consistent with the pathology of pneumonia or ARDS without an identifiable cause
AND
4. No alternative diagnosis can fully explain the illness
Laboratory Case Definition for SARS
1. Nucleic acid testing—Reverse transcriptase polymerase chain reaction (RT - PCR), positive for SARS-CoV using a validated method from:
At least two different clinical specimens (e.g., nasopharyngeal and stool)
OR
The same clinical specimen collected on two or more occasions during the course of the illness (e.g., sequential nasopharyngeal aspirates)
OR
Two different assays or repeat RT-PCR using a new RNA extract from the original clinical sample on each occasion of testing
2. Seroconversion by ELISA or IFA*
Negative antibody test on acute serum followed by positive antibody test on convalescent serum tested in parallel
OR
Fourfold or greater rise in antibody titer between acute and convalescent phase sera tested in parallel
3. Virus isolation
Isolation of the virus in cell culture from any clinical specimen and identification of SARS-CoV using a validated method such as RT-PCR

*Virus neutralization to exclude cross reactions with other human and/or animal coronaviruses is recommended during the inter-epidemic period or when the results of nucleic acid and serologic testing are difficult to interpret.
ARDS, acute respiratory distress syndrome; CoV, coronavirus; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; RNA, ribonucleic acid.

critical in elucidating the likelihood of SARS. Patients with direct and unprotected exposure to a known SARS case are at high risk for disease; travelers returning from a SARS affected area, particularly if they have not come into contact with the health care system or with ill health care workers, are unlikely to have SARS.[47] Fever is the cardinal finding in SARS and is present >97% of patients at presentation. The absence of fever or of a history of fever makes SARS unlikely, particularly if the patient has been sick for 4 to 5 days.[47,63] Rhinorrhea, productive cough, and sore throat are uncommon in microbiologically proven SARS.[47] Radiographically, cavitary disease, adenopathy, and pleural effusions are uncommon in SARS as is interstitial disease, a common presentation of other viral pneumonias.[55,56] Although routine biochemical and hematological tests are not useful in diagnosis, an elevated neutrophil count may lower the probability of SARS to some extent, largely due to the typical neutrophilia associated with community-acquired pneumonia.[85]

Following the initial assessment and admission to hospital, the patient's course of illness is the most important diagnostic clue. The rapid resolution of fever and malaise, stabilization of the chest x-ray, and improvement in lymphopenia after initiation of antibiotic therapy make SARS unlikely.[89,90] Repeated clinical and radiographic assessment is useful in improving clinical diagnosis, and almost all SARS patients develop progressive illness during the first few days of hospitalization, despite treatment with antibiotics.[61,86,91]

Microbiological Diagnosis

Given the difficulty of clinical diagnosis, rapid and accurate confirmatory testing for SARS is essential. Rapid confirmation is critical in the interepidemic period because the detection of even a single case mandates an immediate and concerted effort to identify the source of infection and all infectious contacts and to institute public health and infection-control measures designed to interrupt transmission. In this context, both false-negative and false-positive results have major implications for the patient and the community. When a case of SARS is suspected based on clinical or epidemiological grounds, public health authorities should be contacted immediately and can assist in directing the diagnostic workup. Guidance on diagnostic testing is available online from the WHO.[92,93]

Options for the confirmation of SARS include isolation of the virus, detection of viral ribonucleic acid (RNA), or detection of an antibody response. Virus isolation using cell culture is important in the diagnosis of SARS but has lower sensitivity than other methods, requires several days to obtain results, and must be performed in a laboratory with biosafety level III capability.[94]

Serologic detection of an antibody response to SARS-CoV is the gold standard for the diagnosis of SARS. A variety of techniques can be used, most notably indirect immunofluorescence assay (IFA) and enzyme-linked immunosorbent assay (ELISA). Although cross-reactivity with common human coronaviruses does not appear to be a problem, some animal and market workers in southern China are seropositive due to exposure to SARS-like coronaviruses.[14,94,95] Positive serological tests should be confirmed with neutralization assays. Seroconversion occurs in 50% of patients by day 10, with >90% of patients seroconverting only after 21 to 28 days of illness.[54,96–98] Seroconversion may be delayed in patients taking corticosteroids. Although serologic methods are sensitive and specific they do not provide results rapidly enough to guide initial management.

Detection of viral RNA can be achieved using nucleic acid amplification tests, most commonly reverse transcriptase polymerase chain reaction (RT-PCR).[96,97,99] These methods provide rapid results and can be used within the first week of illness. They are therefore the test of choice for early confirmation of SARS. Sensitivity is 80 to 90% at day 9 to 12 of illness but is less than 40% before day 5 or after day 15.[54,94,96] Newer-generation tests have been developed since the outbreak. In one study in which a real-time PCR assay with improved RNA extraction was compared with first-generation RT-PCR, positivity in the first 3 days was improved from 44 to 80%.[100] Stool and lower respiratory tract specimens have the highest yield.

Although both serology and RT-PCR have high specificity, even tests with high specificity may yield false-positive results when the prevalence of disease is very low. Thus any positive test for SARS in a nonoutbreak setting should be immediately confirmed in a second laboratory using a different methodology.

When SARS is suspected, respiratory samples (e.g., nasopharyngeal swabs or aspirates) should be sent for PCR and culture; plasma or serum should be sent for acute phase serology, PCR, and culture; and stool should be sent for PCR and culture in the first week of illness. The same specimens can be sent again in the second week, and serology should be repeated after 3 and 4 weeks to evaluate seroconversion. Appropriate personal protective equipment, hand washing, and careful adherence to infection control guidelines are essential when collecting, transporting, and handling specimens. Routine collection of lower respiratory tract specimens may not be appropriate given the risk of transmission associated with bronchoscopy. The WHO recommends that all specimens be divided into three aliquots to allow testing at the local, national, and international level.

The greatest challenge currently in SARS diagnosis is the recognition of cases in the interepidemic

period. The WHO and Centers for Disease Control and Prevention (CDC) recommendations on when to perform diagnostic testing are presented in Table 2. Because a diagnosis of SARS is unlikely in the interepidemic period, and because an etiological agent is identified in < 50% of cases with community-acquired pneumonia, it is difficult to balance the need to conduct appropriate surveillance to ensure that another large SARS outbreak is prevented with the desire to avoid the unnecessary concern and expense generated by false-positive tests for SARS. Both guidelines suggest focusing on patients with an epidemiological risk factor for SARS combined with a typical clinical presentation and the lack of an alternative explanation.

When a patient presents with a febrile respiratory tract illness, a travel and exposure history should be taken. In patients at risk for SARS (e.g., laboratory workers working with SARS-CoV, travelers from southern China exposed to exotic animals) presenting with compatible clinical and radiographic findings, attempts should be made to identify other causes of pneumonia. If progression occurs despite antibiotic treatment and no alternative diagnosis is made, public health authorities should be contacted and testing for SARS-CoV initiated. Because of our limited ability to make early and rapid diagnoses, all patients with unexplained febrile respiratory illnesses should be cared for using droplet and contact precautions.

Table 2 Testing for SARS in the Interepidemic Period: Centers for Disease Control and Prevention and World Health Organization Recommendations

CDC RECOMMENDATIONS

Severe respiratory illness in the context of a documented exposure risk is the key to diagnosing SARS-CoV disease.

Providers should therefore consider SARS-CoV disease in patients requiring hospitalization for:

- Radiographically confirmed pneumonia or acute respiratory disease syndrome of unknown etiology, AND
- One of the following risk factors in the 10 days before illness onset:
  - –Travel to mainland China, Hong Kong, or Taiwan, or close contact with an ill person with a history of recent travel to one of these areas, OR
  - –Employment in an occupation associated with a risk for SARS-CoV exposure (e.g., health care workers with direct patient contact; worker in a laboratory that contains live SARS-CoV), OR
  - –Part of a cluster of cases of atypical pneumonia without an alternative diagnosis

WHO RECOMMENDATIONS

A SARS Alert should be signaled and appropriate diagnostic tests performed on any patient meeting the following criteria:

1. An individual with clinical evidence of SARS* AND with one or more of the following epidemiological risk factors for SARS-CoV infection in the 10 days before the onset of symptoms:
   - Employed in an occupation associated with an increased risk of SARS-CoV exposure (e.g., staff in a laboratory working with live SARS-CoV/SARS-CoV-like viruses; persons with exposure to wildlife or other animals considered a reservoir of SARS-CoV, their excretions or secretions, etc.)
   - Close contact (having cared for, lived with, or had direct contact with the respiratory secretions or bodily fluids) of a person under investigation for SARS
   - History of travel to, or residence in, an area experiencing an outbreak of SARS

OR

2. Two or more health care workers with clinical evidence of SARS in the same health care unit and with onset of illness in the same 10-day period

OR

3. Three or more persons (health care workers and/or patients and/or visitors) with clinical evidence of SARS with onset of illness in the same 10-day period and epidemiologically linked to a health care facility

Clinical Evidence

A clinical case of SARS is an individual with:

1. A history of fever, or documented fever $\geq 38^{\circ}C$

AND

2. One or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath)

AND

3. Radiographic evidence of lung infiltrates consistent with pneumonia or ARDS or autopsy findings consistent with the pathology of pneumonia or ARDS without an identifiable cause

AND

4. No alternative diagnosis can fully explain the illness

ARDS, acute respiratory distress syndrome; CoV, coronavirus; SARS, severe acute respiratory syndrome.

MANAGEMENT OF THE SARS PATIENTS

General Measures

Patients with suspected SARS should be admitted to hospital and managed using droplet and contact precautions. If the clinical presentation is consistent with bacterial pneumonia, antibiotics appropriate for the treatment of community-acquired pneumonia should be initiated. Patients with SARS that are hypoxemic at presentation and patients with prognostic features predictive of poor outcome, particularly advanced age, should be placed in a monitored setting to allow early intubation under controlled circumstances. The risk of pneumothorax and pneumomediastinum in mechanically ventilated SARS patients may be as high as 20 to 40%, which is significantly higher than the incidence with other causes of ARDS.[57,58,101] If mechanical ventilation is required a low-volume, low-pressure ventilation strategy should be used.[57,58]

Specific Therapies

Several specific therapies intended to reduce SARS-CoV replication or to modulate the immune system were used during the global SARS outbreak. The two most commonly used agents were ribavirin and corticosteroids; therapies used in smaller numbers of patients included interferon alfacon-1, lopinavir/ritonavir, intravenous immunoglobulin (IVIG), convalescent serum, and exchange transfusion. In addition, a variety of traditional Chinese medications were used in China and Hong Kong.

Ribavirin is an antiviral drug that was used early in the SARS outbreak because of its wide spectrum of antiviral activity against RNA and DNA viruses. Small studies conducted early in the outbreak using surrogate outcomes suggested some benefit from this agent[102] but these benefits were not seen in subsequent, larger studies.[38,72,103] None of these studies were controlled. Several reports described frequent and severe adverse events associated with ribavirin use, including the development of severe hemolytic anemia in 49 to 73% of patients.[38,68,104,105] In vitro studies suggested that ribavirin does not have activity against SARS-CoV at clinically achievable doses,[106–109] and autopsy studies demonstrated that ribavirin-treated patients still had viable, replicating virus.[110]

Corticosteroids were also used throughout the outbreak, often in conjunction with ribavirin. Respiratory failure in SARS often occurred after the peak in viral load, suggesting the possibility of immune-mediated lung damage and providing a rationale for the use of corticosteroids.[54] Conversely, persistently high viral loads found in lung tissue despite prolonged illness raised the concern that corticosteroid use could increase or prolong viral replication.[110,111] Initial studies demonstrated improvement in surrogate end points such as fever and radiographic findings but subsequent studies noted progression despite corticosteroid use.[39,112,113] Similarly, the use of pulsed corticosteroids appeared beneficial in some studies and was associated with increased mortality in others.[113,114] Again, none of these studies was controlled. Adverse events associated with prolonged high-dose steroid therapy for SARS included fungal superinfection[89,115,116] and avascular osteonecrosis.[117–119]

For the other agents used in SARS, even fewer data on efficacy are available. In vitro data demonstrate some activity for interferons, particularly interferon β. One study of interferon-alfacon-1 combined with pulsed steroids when compared with historical controls treated with lower doses of corticosteroids suggested an improvement in surrogate clinical end points.[120] Lopinavir/ritonavir also shows some in vitro activity and appeared effective compared with historical controls treated with ribavirin and steroids.[109,121] A systematic review of traditional Chinese medications used in SARS found poor methodology in all studies and was unable to confirm the efficacy of any of these agents.[122] Other agents in SARS were used primarily as rescue therapy in small numbers of patients, and data on efficacy are not available.

Currently there are no data from controlled, clinical trials supporting the use of any specific agent for SARS. Should future cases occur, only patients at risk of adverse outcomes should be treated with these agents, ideally in the context of a clinical trial. Patients under 60 years of age without any poor prognostic factors would be expected to recover spontaneously from SARS and are unlikely to benefit from treatment.

INFECTION CONTROL

SARS was frequently transmitted in the hospital. When SARS is suspected, preventing transmission to patients, visitors, and health care workers is a key priority and will reduce the number of secondary cases and therefore the total morbidity and mortality associated with any outbreak.

The first step in preventing SARS transmission is for all front-line health care workers to recognize that all patients with febrile respiratory illness may have SARS or another transmissible infectious agent. Patients with fever and respiratory symptoms should be placed in droplet and contact isolation unless an airborne pathogen such as tuberculosis is suspected and until either a specific diagnosis is made or their illness resolves. This universal approach will minimize the transmission of SARS even when the diagnosis is not initially suspected.

The second step in preventing SARS transmission requires that clinicians remain aware of SARS during the interepidemic period. Early diagnosis is

critical because effective public health measures cannot be initiated until the first case is recognized. Early diagnosis requires a high index of suspicion, an awareness of the clinical features and epidemiological risk factors for SARS, and knowledge of the current status of SARS transmission globally.

When cases of suspected or confirmed SARS are identified, additional precautions should be taken to further reduce transmission. Patients should be isolated in a single room and placed in droplet and contact precautions, which should include the use of gowns, gloves, masks, eye protection, and hand washing. Some studies suggest that N95 masks are preferred to surgical masks, although in most instances surgical masks appeared sufficient to interrupt transmission.[37,41] Because airborne transmission has not definitively been ruled out, negative-pressure isolation rooms should be used if available. Procedures that involve airway manipulation (e.g., intubation, bronchoscopy, nebulized therapy, suction) should be used only if clinically indicated and should be performed by experienced health care workers under controlled conditions and with only essential personnel present. All health care workers providing care should receive additional instruction about the equipment and precautions to be used. In most instances when health care workers were infected following these procedures, evidence of a breach in standard infection control precautions has been noted (e.g., failure to wear eye protection, lack of consistent hand hygiene, etc.).

The recognition of even a single case of probable SARS should prompt the immediate activation of local, national, and international public health strategies to contain SARS. Local public health authorities, once notified, will begin contact tracing to ensure that additional undiagnosed cases do not cause ongoing transmission. If the patient was a traveler, notification of the countries of origin and identification of fellow travelers will be critical in preventing or limiting spread. If the patient was not a traveler, the chain of transmission must be traced backward to identify the index case, who will most likely be a traveler, a laboratory worker, or someone with direct contact with exotic animals in southern China.

CONCLUSIONS

Considerable progress has been made in understanding the origins of SARS and the likelihood of another pandemic. Although SARS-CoV-like viruses are likely to continue to affect the human population, careful attention to the lessons learned from the first global SARS pandemic should prevent major outbreaks in the future. The prevention of future outbreaks requires ongoing vigilance, both by public health authorities and by front-line clinicians, who must remain aware of epidemiology and clinical features of SARS to ensure the earliest possible recognition of the next case or clusters of SARS.

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