LEADING ARTICLE

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Severe Acute Respiratory Syndrome

Pertinent Clinical Characteristics and Therapy

Thomas M. File Jr[1,2] and *Kenneth W.T. Tsang*[3]

1 Northeastern Ohio Universities College of Medicine, Rootstown, Ohio, USA
2 Infectious Disease Service, Summa Health Service, Akron, Ohio, USA
3 University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

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 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.

Severe acute respiratory syndrome (SARS) was first recognized in the Guangdong Province in Southeast China in late 2002, and it subsequently spread globally rapidly during the early months of 2003.[1,2] SARS captured worldwide attention as a highly infectious disease with high mortality and as an occupational hazard among healthcare providers. The impact of SARS was extensive from both a sociological and economical consequence – particularly in Asia. Because the causative agent of SARS is contagious, preventative measures focus on avoidance of exposure, and infection control strategies for suspected patients and contacts. The emergence of SARS illustrates the need for global cooperation of healthcare systems to ensure the public health of local regions, and the need to be prepared to rapidly institute policies to respond to newly emerging infectious threats.

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.[3,4] A suspect case included a respiratory illness of unknown etiology and with the following criteria:

- measured temperature >100.4ºF (>38.0ºC)
- 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 serovonversion, 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[a]
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[b]
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

a Tests to detect SARS-CoV are being refined and, therefore, criteria for laboratory diagnosis of SARS-CoV are changing.
b Asymptomatic infection or clinical manifestations other than respiratory illness may be identified in future as more is learned about SARS-CoV.
CDC = Center for Disease Control; **RT-PCR** = reverse transcription polymerase chain reaction; **SARS-CoV** = SARS-associated coronavirus.

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] Some healthcare workers also appeared to have acquired SARS via contact with a fomite. Of still unexplained significance, a few patients have been involved in the transmission of an unusually large number of secondary cases – so-called super-spreading events.

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

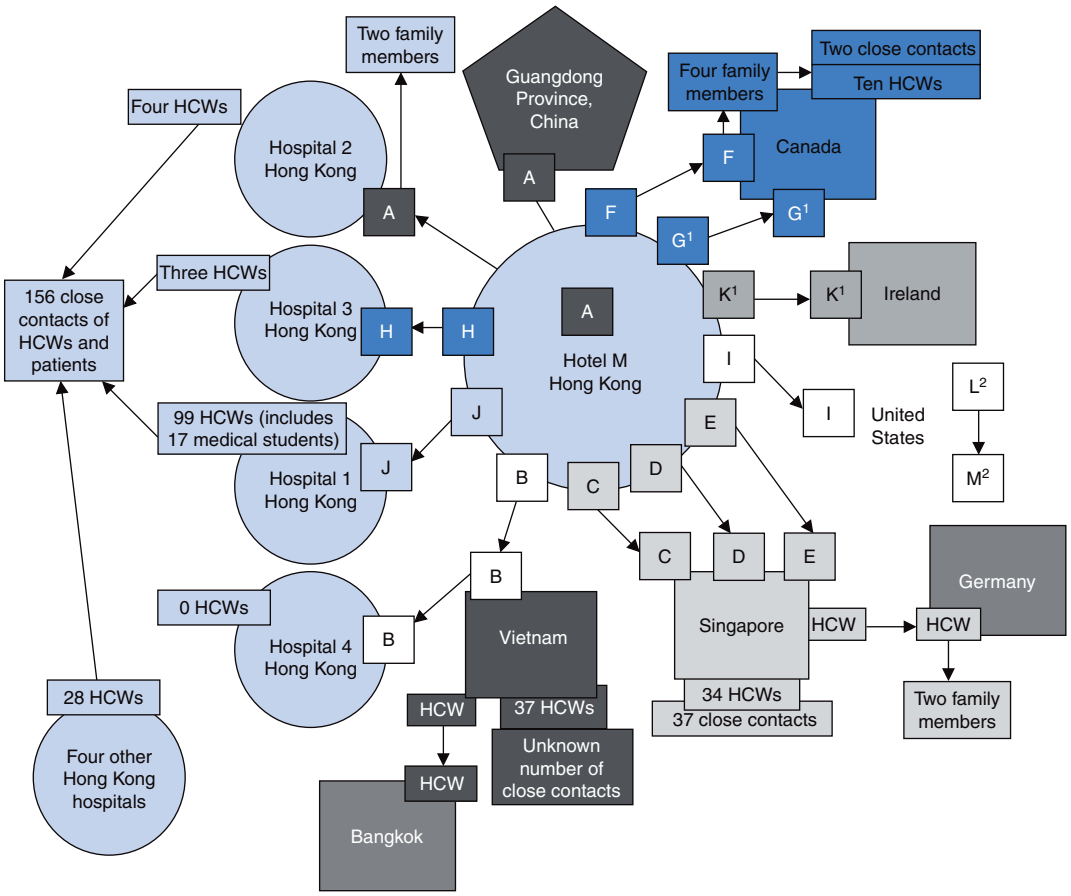

Fig. 1. Schematic presentation of the chain of transmission of virus among guests at hotel 'M' in Hong Kong in 2003.[14] **1** All guests except G and K stayed on the 9th floor of the hotel. Guest G stayed on the 14th floor and guest K stayed on the 11th floor. **2** Guests L and M (spouses) were not at hotel M during the same time as index guest A, but were at the hotel during the same times as guests G, H and I, who were ill during this period. **HCW** = healthcare workers.

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.[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.[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 laboratory-confirmed cases). At the time of writing, a total of nine possible cases of SARS have been identified and the health authorities were involved in active surveillance to identify other possible cases.[20]

4. Clinical Manifestations

The initial descriptions of the clinical manifestations of SARS have come from reports of patients who have required hospitalization.[8,21-24] In such patients the disease is often reported as a biphasic 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

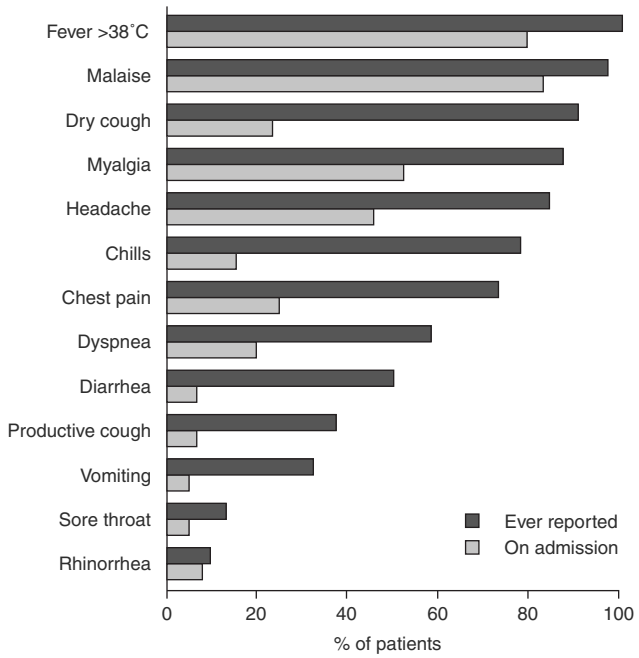

Fig. 2. Symptoms of 62 patients with severe acute respiratory syndrome, at hospital admission and reported during the course of illness, during the period February–May 2003.[27]

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 $\times$ 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

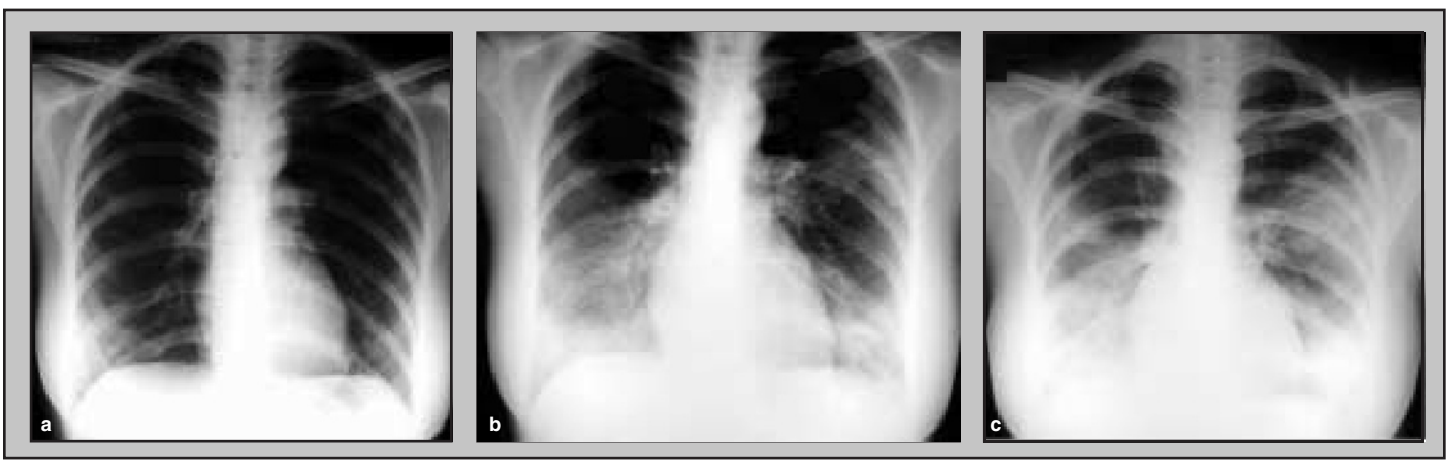

Fig. 3. Serial chest x-ray findings in a 28-year-old woman with severe acute respiratory syndrome. The patient presented acutely 3 days after onset of a high fever, and was immediately hospitalized upon attendance at the Accident and Emergency Department. (**a**) Mild ground glass consolidation of the right lower lobe when the patient was relatively free of respiratory symptoms and did not require oxygen therapy on day 1; (**b**) overnight deterioration in clinical status with increasing oxygen requirement to 4 L/min and development of bilateral consolidation on day 2; (**c**) progressive respiratory failure and worsening of chest x-ray findings on day 3.

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[a]			
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[b]			
Serum	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.[33] 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.,[8] 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.[35] 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 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]

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

Table VI. Recommendations for the evaluation of patients with community-acquired respiratory illness in the presence or absence of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) transmission in the world[34]

In the absence of SARS-CoV transmission anywhere in the world, the diagnosis of SARS-CoV disease should be considered only in patients who require hospitalization for radiographically confirmed pneumonia and who have an epidemiologic history that raises the suspicion of SARS-CoV disease.
In the absence of SARS-CoV transmission anywhere in the world, suspicion of SARS infection is raised if, within 10 days of symptom onset: the patient had a history of recent travel to mainland China, Hong Kong, or Taiwan; was in close contact with ill people with a history of recent travel to such areas; is employed in an occupation at particular risk for SARS-CoV exposure, including a healthcare worker with direct contact or a worker in a laboratory that contains live SARS-CoV; or is part of a cluster of cases of atypical pneumonia without an alternative diagnosis
Once SARS-CoV transmission has been documented in the world, a diagnosis of SARS should still be considered in patients who require hospitalization for pneumonia and who have an epidemiologic history described above. In addition, all patients with fever or respiratory symptoms should be questioned about whether within 10 days of symptom onset they have had: close contact with someone suspected of having SARS-CoV disease; a history of foreign travel (or close contact with an ill person with a history of travel) to a location with documented or suspected SARS-CoV infection; exposure to a domestic location with documented suspected SARS-CoV (including a laboratory that contains live SARS-CoV); or close contact with an ill person with such an exposure history

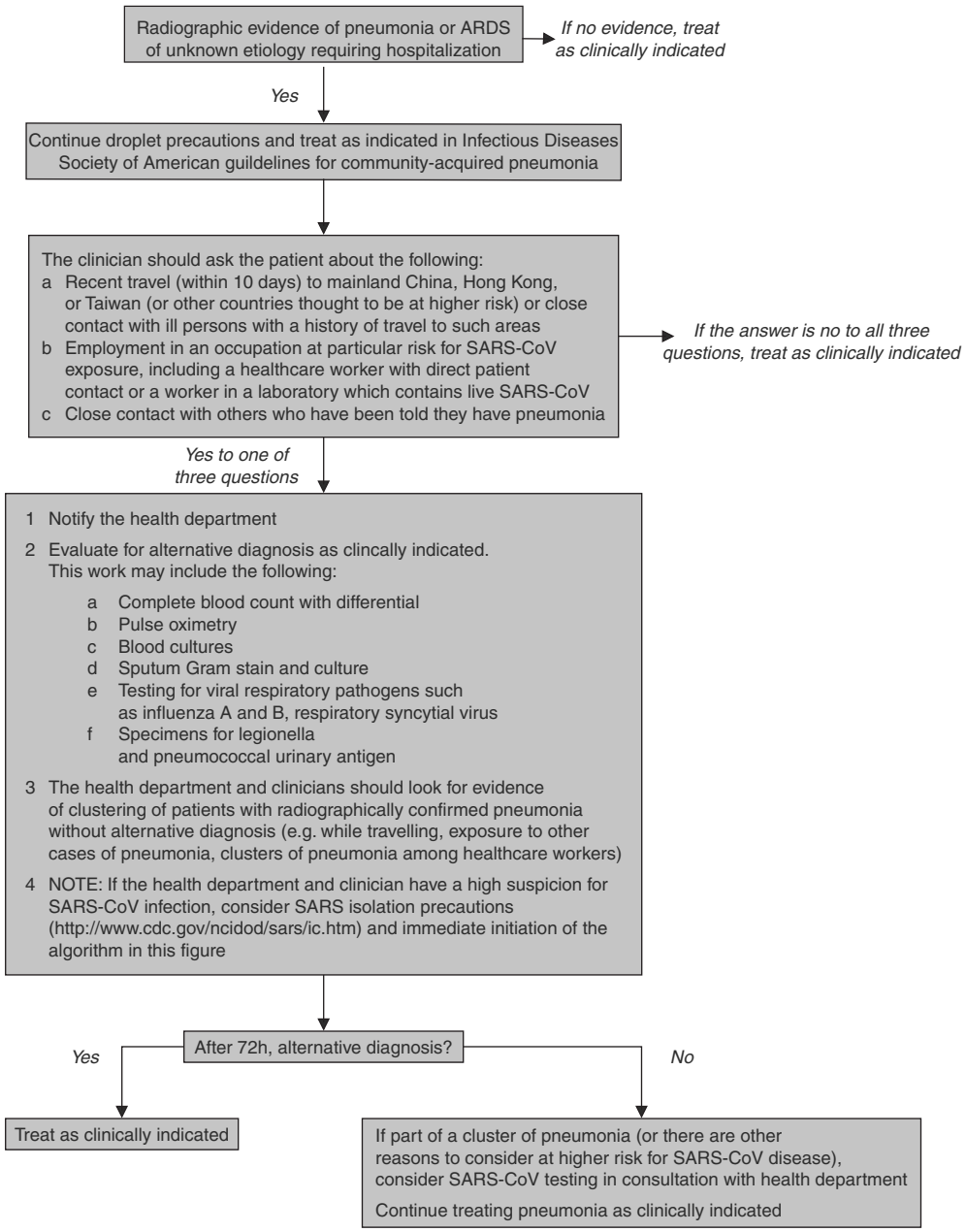

Fig. 4. Algorithm for evaluating and managing patients requiring hospitalization for radiographically confirmed pneumonia, in the absence of person-to-person transmission of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) anywhere in the world.[34]

measures centered on avoidance of exposure and infection. Such measures include global and regional surveillance, early detection of new cases, identification of patient contacts, and strict adherence to infection control policies. Guidelines for infection control have been published and should be consulted for updated recommendations.[34,39] Healthcare workers encountering a possible case of SARS (suspected or probable) should take meticulous safety precautions and seek advice from an expert in SARS infection control.

Hospitalized patients with suspected SARS should be isolated in negative pressure rooms; healthcare workers should wear masks (a high efficiency mask such as the N-95 respirator used for tuberculosis) to prevent air-droplet and airborne acquisition. Because coronaviruses can survive on environmental surfaces, good hand-washing with soap and water or use of an alcohol-based hand rub is highly recommended as well. Environmental surfaces that are frequently touched by the patient or are soiled with body fluids should be cleaned and disinfected with a household disinfectant.

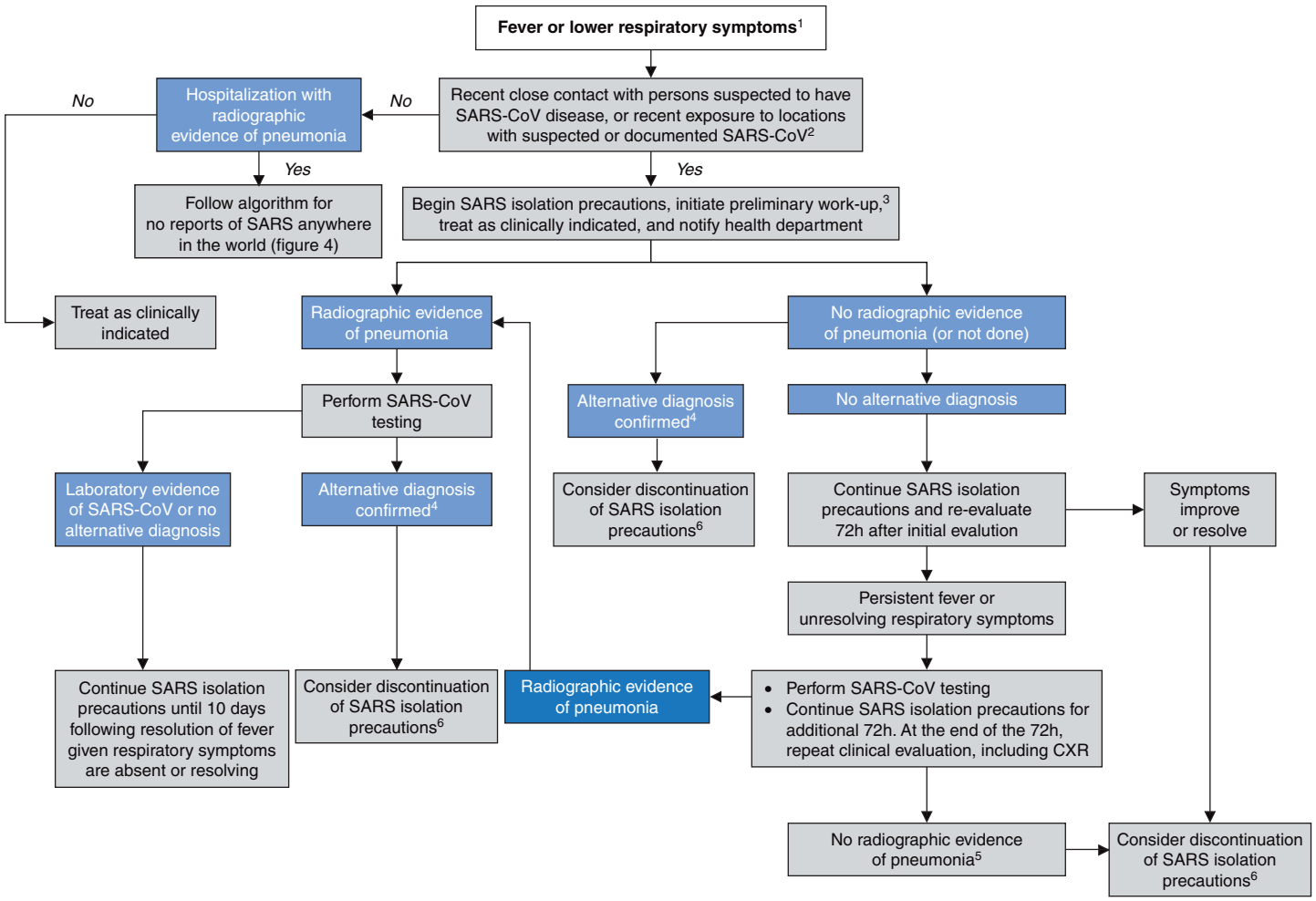

Fig. 5. Algorithm for the management of fever or respiratory symptoms in patients when person-to-person transmission of severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) has been documented in the world.[34] **1** The early symptoms of SARS-CoV disease usually include fever, chills, rigors, myalgia, and headache. Respiratory symptoms often do not appear until 2–7 days after the onset of illness. **2** In settings with more extensive transmission, all patients with fever or respiratory symptoms should be evaluated for possible SARS-CoV disease. **3** Depending on symptoms and exposure history, initial diagnostic testing for patients may include complete blood count, chest x-ray (CXR), pulse oximetry, blood cultures, sputum Gram stain and culture, testing for viral respiratory pathogens (notably influenza and respiratory syncytial virus), *Legionella* sp. and pneumococcal urinary antigen. **4** An alternative diagnosis should be based on laboratory tests with high-predictive value (e.g. blood culture, urinary antigen). **5** Chest computed tomography (CT) may show evidence of an inflitrate before a CXR. Therefore, a chest CT should be considered in patients with a strong epidemiologic link to a known case of SARS and a negative CXR 6 days after onset of symptoms. **6** SARS isolation precautions should be discontinued after consultation with local public health authorities and the evaluating physician.

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-

sence of fever or respiratory symptoms, they need not limit their activities.

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).[40] 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.[34] 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 SRS-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.[19] 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 (≥38ºC) and community-acquired pneumonia are admitted to isolation wards to exclude SARS.[20] 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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Correspondence and offprints: Professor *Thomas M. File*, Jr, Infectious Disease Service, Summa Health Service, Suite 105, 75 Arch St, Akron, 44304 OH, USA.

E-mail: filet@summa-health.org