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Infectious Diseases

## Severe Acute Respiratory Syndrome (SARS)

SARS

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### Management Highlights

- Consider the diagnosis of severe acute respiratory syndrome (SARS) in a patient who presents with fever, with or without lower respiratory tract symptoms, and with a history of recent travel or potential exposure to SARS within the past 10 days; otherwise, assess the patient for more likely diseases, such as acute bronchitis or community-acquired pneumonia (CAP) unrelated to the SARS virus.
- Suspect CAP in a patient who presents with an acute onset of fever (or hypothermia), cough (dry or productive), dyspnea, and/or chest discomfort, and who on physical examination has tachypnea (more than 25 breaths per minute), bronchial breath sounds, and/or rales.
- Obtain a chest x-ray in patients at risk for SARS (those with fever and potential SARS exposure within the preceding 10 days, with or without lower respiratory tract symptoms or signs); if a patient with suspected SARS has a negative chest x-ray, consider obtaining high-resolution CT of the thorax.
- In a patient with suspected SARS, obtain a CBC and chest x-ray; if the chest x-ray is normal, do not routinely order any additional laboratory tests.
- In a patient with probable SARS, obtain specimens to exclude treatable causes of CAP, such as two blood cultures, a cold-agglutinin test, a *Mycoplasma pneumoniae* immunoglobulin M titer, a *Legionella* urine antigen test, and HIV serology; as needed, include pulse oximetry, sputum Gram stain and culture, and tests for influenza A and B and respiratory syncytial virus.
- In a patient with probable SARS, consider obtaining a CBC, platelet count, creatinine phosphokinase, liver enzyme (transaminase) tests, urea, electrolytes, and C reactive protein to help identify potential laboratory clues to SARS.

- In general, consider invasive procedures, such as fiberoptic bronchoscopy (with or without transbronchial biopsy), only to evaluate patients with probable SARS if they have progressive deterioration and fail to respond to therapy and you suspect serious treatable comorbidity or an alternative diagnosis.
- Report a patient with suspected or probable SARS to the appropriate health department, and ask about specific testing (serologic, reverse transcription polymerase chain reaction [RT-PCR], culture) for the SARS virus.
- Diagnose suspected SARS in a patient who meets Centers for Disease Control and Prevention (CDC) clinical criteria for idiopathic moderate respiratory illness (temperature above 38 °C [100.4 °F] plus cough, dyspnea, or hypoxia) and CDC epidemiologic criteria (onset within 10 days of potential exposure; <http://www.cdc.gov/ncidod/sars/casedefinition.htm>).
- Diagnose probable SARS in a patient who meets the CDC criteria for suspected SARS and has at least one of the following: x-ray evidence of pneumonia, (acute) respiratory distress syndrome, or compatible otherwise unexplained autopsy findings.
- For patients with suspected SARS, consider following the World Health Organization (WHO) recommendations of immediate triage, surgical mask, detailed history (travel, contacts), CBC, and chest x-ray, followed by hospitalization of patients with unilateral or bilateral infiltrates on chest x-ray.
- Use careful infection-control measures in caring for patients with suspected SARS: hand washing, eye protection, gloves, gowns, and N-95 filtering disposable respirators.
- Strongly consider consulting an infectious disease specialist and/or pulmonologist for all patients with probable SARS, especially before initiating potentially toxic and unproven specific antiviral (ribavirin) or corticosteroid therapy.
- Admit SARS patients to the intensive care unit if they require mechanical ventilation for respiratory failure (evidenced by breathing rate above 35 breaths per minute, arterial oxygen pressure less than 90% on 50% supplemental oxygen, systolic blood pressure less than 90 mmHg) or for hemodynamic support and close monitoring.
- Intubate and mechanically ventilate SARS patients with respiratory failure who do not adequately respond to noninvasive supplemental oxygen and respiratory support measures.
- If applicable, review recent CDC or WHO information about avoiding SARS transmission in special settings (<http://www.cdc.gov/ncidod/sars/exposureguidance.htm>) or related to travel ([http://www.cdc.gov/travel/other/acute\\_resp\\_syn\\_multi.htm](http://www.cdc.gov/travel/other/acute_resp_syn_multi.htm)).
- Until 10 days after fever and respiratory symptoms have resolved, advise outpatients with suspected SARS to continue infection-control precautions,

including limiting social interactions, practicing regular hand hygiene, wearing a surgical mask, and frequently using household cleaners ([www.cdc.gov/ncidod/sars/ic-closecontacts.htm](http://www.cdc.gov/ncidod/sars/ic-closecontacts.htm)).

- Consider hospital discharge for a convalescent SARS patient with no fever for 48 hours, resolving cough, normalized laboratory studies, and improving chest x-ray abnormalities.
- Instruct discharged convalescent patients to measure and record their temperature twice daily; to remain at home, stay indoors, and minimize contact with others; and to return for a follow-up visit in 1 week.

## Background

### Overview

**Use this article for information about diagnosing and managing a patient with suspected SARS.**

SARS is a rapidly progressive, sometimes fatal atypical pneumonia caused by a newly identified coronavirus (called the SARS coronavirus). SARS seems to have arisen in Guangdong Province in southern China, where the first suspicious cases of unexplained atypical pneumonia appeared in November 2002 [1]. On March 12, 2003, the WHO issued a global alert on an unexplained atypical pneumonia, called SARS, after an outbreak of pneumonia was reported in a public health hospital in Hong Kong. About the same time, the WHO received case reports of a similar progressive atypical pneumonia syndrome from China, Singapore, Thailand, Vietnam, Indonesia, Taiwan, the Philippines, Canada, Germany, and the United States.

Although the cumulative number of suspected cases and number of countries reporting cases continue to increase, both Vietnam and Canada have apparently stopped the spread of the infection by instituting vigorous infection-control measures. Also, by the end of April 2003, the overall worldwide incidence of reported new cases of SARS had continued to decrease from the peak at the end of March 2003. The health effects of SARS so far are relatively minor, compared with those of diseases such as malaria and HIV infection/AIDS, which each kill millions of people worldwide annually. In contrast, the psychological, social, economic, and political ramifications of this new disease have been disproportionately large; those topics are beyond the scope of this article.

**Clinical presentation and transmission:** Patients with SARS typically present with high fever, systemic symptoms, and one or more respiratory symptoms (dry cough, shortness of breath, or difficulty breathing). SARS seems to be spread mainly by respiratory droplets, and serologic studies so far indicate that people in the worldwide general population have not had prior exposure and have no serologic immunity (detectable antibodies) to the SARS virus.

**Diagnosis:** The diagnosis of suspected or probable SARS is based at present on clinical and epidemiologic data. Although several of the tests, especially reverse-transcriptase polymerase chain reaction (RT-PCR), for SARS virus infection that are undergoing trials at present seem to have high specificity, their sensitivity is still unproven and the tests are as-yet insufficiently standardized to be included as diagnostic criteria in standard guidelines. Also, because RNA viruses such as the SARS virus mutate frequently, a test that may be very accurate in a given cohort may be inaccurate in another cohort, because the strains of SARS virus are different in different cohorts. Thus, a negative test for SARS virus does not necessarily rule out infection with SARS virus.

**Differential diagnosis:** Because the clinical manifestations of SARS in individual patients are not clearly distinguishable from the manifestations of atypical, or even typical, pneumonia caused by other microbial pathogens, clinicians should consider SARS in any patient who presents with an acute onset of fever and evidence of lower respiratory tract infection. In at least one clinical series, the two best predictors of SARS were high fever and exposure to a suspected or probable SARS patient within the preceding 10 days.

**Clinical course:** After a 2- to 10-day incubation period, a typical SARS patient develops a fever (higher than 38 °C, or 100.4 °F) with nonspecific systemic symptoms (myalgias, chills, headache), followed in 2 to 7 days by lower respiratory tract symptoms (dry, nonproductive cough; shortness of breath), which may progress to dyspnea and hypoxemia. About 20% to 40% of such patients will require intensive care unit admission, and 10% to 20% will require mechanical ventilation [2].

**Management:** The CDC recommends managing patients with SARS essentially in the same way as any other patient with serious community-acquired atypical pneumonia of unknown cause [3]. However, because of the high infectivity of the SARS virus, the uncertain modes of transmission, and the absence of immunity in the healthcare and general community, vigorous infectious-droplet-control measures, including wearing of masks and rigorous disinfection and hygiene procedures, are now considered to be particularly important when caring for patients with suspected or probable SARS [1].

**Antiviral treatment:** Although major groups in Hong Kong with extensive experience in managing SARS patients advocate hospitalization and the use of intravenous ribavirin and corticosteroids to treat probable SARS patients (those with abnormal chest x-rays or high-resolution CT scans), other authorities question the efficacy of this or any antiviral therapy now available for SARS patients [4].

**Internet updates:** Because of the rapid pace of developments in the understanding, worldwide spread, diagnosis, and management of SARS patients, it is advisable check the Internet sites listed in this article for the latest

information, before making any significant management decisions pertaining to individual patient care [Table 1]. Many of the sites are updated at least weekly, so they represent the most practical source for current credible information. Both the WHO general SARS site and the CDC general SARS site include a vast amount of up-to-date information for clinicians, and links to other credible sites [Table 1].

<b>Table 1: SARS Internet Sites</b>	
<b>Organization</b>	<b>URL</b>
<b>General/Comprehensive Patient and Professional Information</b>	
WHO	<a href="http://www.who.int/csr/sars/guidelines/en/">http://www.who.int/csr/sars/guidelines/en/</a> (general) <a href="http://www.who.int/csr/sarscountry">http://www.who.int/csr/sarscountry</a> (cumulative cases) <a href="http://www.who.int/csr/sars/casedefinition/en">http://www.who.int/csr/sars/casedefinition/en</a> (case definition) <a href="http://www.who.int/csr/sars/management/en/">http://www.who.int/csr/sars/management/en/</a> (treatment)
CDC	<a href="http://www.cdc.gov/ncidod/sars/clinicians.htm">http://www.cdc.gov/ncidod/sars/clinicians.htm</a> (general) <a href="http://www.cdc.gov/ncidod/sars/casedefinition.htm">http://www.cdc.gov/ncidod/sars/casedefinition.htm</a> (case definition) <a href="http://www.cdc.gov/ncidod/sars/travel.htm">http://www.cdc.gov/ncidod/sars/travel.htm</a> (travel advisory) <a href="http://www.cdc.gov/ncidod/sars/index.htm">http://www.cdc.gov/ncidod/sars/index.htm</a> (infection control guidelines) <a href="http://www.cdc.gov/ncidod/sars/ic-closecontacts.htm">http://www.cdc.gov/ncidod/sars/ic-closecontacts.htm</a> (infection control measures for outpatients)
MMWR	<a href="http://www.cdc.gov/mmwr">http://www.cdc.gov/mmwr</a>
US AMA	<a href="http://www.ama-assn.org/ama/pub/article/1949-7564.html">http://www.ama-assn.org/ama/pub/article/1949-7564.html</a> (many links to SARS updates and information)
Canada (CMAJ)	<a href="http://cmaj.ca">http://cmaj.ca</a> (Tracks ongoing developments in SARS)
Health Canada	<a href="http://www.hc-sc.gc.ca/pphb-dgsp/sars-sras/prof_e.html">http://www.hc-sc.gc.ca/pphb-dgsp/sars-sras/prof_e.html</a> (includes infection control measures)
UK PHLS	<a href="http://www.phls.co.uk/topics_az/SARS/health_professional_page.htm">http://www.phls.co.uk/topics_az/SARS/health_professional_page.htm</a> (practical guidance for clinicians in UK, but also useful elsewhere)
<b>Miscellaneous</b>	
“Preventing the Spread of Severe Acute Respiratory Syndrome”	<a href="http://www.cdc.gov/ncidod/sars/webcast/broadcast040403.htm">http://www.cdc.gov/ncidod/sars/webcast/broadcast040403.htm</a> (public health infection control training satellite program)_
SARS Watch Org	<a href="http://sarswatch.org/">http://sarswatch.org/</a> (public media coverage)
<b>CDC, Centers for Disease Control; CMAJ, Canadian Medical Association Journal; MMWR, Morbidity and Mortality Weekly Report; UK PHLS, United Kingdom Public Health Laboratory Service; US AMA, United States American Medical Association; WHO, World Health Organization.</b>	

## Etiology/Pathophysiology

**Unique pathogen:** On April 16, 2003, the WHO announced that a new pathogen, a member of the coronavirus family never before identified in humans, is the cause of SARS; they called it the “SARS virus” [5]. The CDC has called it the “SARS-associated coronavirus” (SARS-CoV) [<http://www.cdc.gov/ncidod/sars/casedefinition.htm>]. The National Library of Medicine/International Committee on Taxonomy of Viruses taxonomy officially named this the “SARS coronavirus” [<http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Tree&id=227859&lvl=3&lin=f&keep=1&srchmode=1&unlock>]. Although the close collaborative efforts of 13 laboratories from 10 countries had previously provided many strong associations between this virus and SARS, the Koch’s postulates required for proof of causation were first declared met on April 16, 2003.

**Coronaviruses:** The family *Coronaviridae*, which includes the genera *Coronavirus* and *Torovirus*, are enveloped RNA viruses that cause disease in humans and animals [6]. Two previously identified human coronaviruses (types 229E and OC43) cause about 30% of common colds and can occasionally cause pneumonia in immunocompromised people, older people, military recruits, and neonates. In contrast, several animal coronaviruses are particularly virulent in their respective hosts, in which they can cause respiratory, gastrointestinal, hepatic, or neurological diseases.

**Serology:** Overall, the clinical, biologic, and genetic data have shown that the SARS virus is not one of the known human coronaviruses [6]. For example, antibodies against type 229E and OC43-like coronaviruses are common in the general population. In contrast, in a study that found serologic and/or reverse-transcriptase polymerase chain reaction (RT-PCR)-specific evidence of SARS virus infection in 45 of 50 SARS patients, no antibodies against SARS virus were detected in 80 patients with other diseases or 200 blood donors [6].

**Viral origin:** Presumably the SARS virus originated from animals in China and mutated or recombined in a way that permits it to infect, to cause disease, and to be transmitted from human to human [7]. The epidemiologic data indicate that SARS virus is spread by droplets, or by direct or indirect contact, although airborne spread has not been entirely excluded [6].

**Droplet transmission:** In a retrospective case-control survey study of 241 noninfected and 13 infected hospital staff exposed to 11 index SARS patients, none of the 69 staff members who reported consistently using all four of the recommended infection-prevention measures (mask, gloves, gowns, hand washing) became infected [8]. Whereas use of each individual measure was associated with reduced risk for infection, stepwise logistic regression was significant only for masks. Hand washing and the use of surgical or N95 masks,

but not paper masks, was associated with non-infection. Thus, at least in a hospital setting, the SARS virus seems to be transmitted mainly by droplets.

**Laboratory samples/specimens:** Drosten and colleagues, using a highly sensitive real-time RT-PCR procedure on various specimens from two SARS patients, found high concentrations of viral RNA (up to 100 million molecules/milliliter) in sputum, but extremely low concentrations in plasma, during the acute phase, and in the stool in the convalescent phase [9]. These findings also indicate that shedding of SARS virus from the respiratory tract is the main route of transmission. Notably, the nasal and throat swab specimens contained far less viral RNA than the sputum specimens, which indicates that nasal and throat swabs are less suitable for diagnostic sampling.

**Alternative transmission routes:** Although SARS virus seems to be spread mainly by droplets shed during sneezing or coughing, especially in a hospital setting, various case and cohort studies indicate that other routes of transmission are also involved. A CDC study found that SARS virus could survive for 24 hours on dry surfaces, in feces and urine for 1 to 2 days at room temperature, and in diarrhea for up to 4 days, which indicates that direct or indirect contact transmission is possible [<http://www.who.int/csr/sars/project/en/>; [http://www.who.int/csr/sars/survival\\_2003\\_05\\_04/en/index.html](http://www.who.int/csr/sars/survival_2003_05_04/en/index.html)]. Notably, more than 300 residents of a large apartment complex in Hong Kong developed SARS despite the fact that many of the residents had no apparent contact with each other. The outbreak was unusual in that many of the SARS patients had severe diarrhea, and SARS virus was identified in fecal samples. The health authorities postulated that the transmission was related to breaks in the building's sewer lines [<http://www.info.gov.hk/dh/ap.htm>].

**Postmortem findings:** Although postmortem data are limited, the few reported cases have shown histologic evidence of the early phase of acute (adult) respiratory distress syndrome in the lungs with no evidence of involvement of other organs [9]. However, SARS is commonly associated with increased aminotransferase and lactate dehydrogenase (LDH) levels in the serum, and shedding of virus in the feces, which indicates that SARS virus is replicating outside the respiratory tract.

### Demographics/Epidemiology

As of early May 2003, more than 6000 people worldwide had been diagnosed as having probable SARS, and more than 400 affected patients had died [[http://www.who.int/csr/sarscountry/2003\\_05\\_03/en/](http://www.who.int/csr/sarscountry/2003_05_03/en/)]. Most SARS patients have been ethnic Chinese who live in either China or Hong Kong. Although an inherent genetic vulnerability cannot be excluded, increased risk of exposure is a likely explanation for the high incidence of SARS in this ethnic group. Minor gender differences in SARS incidence may also be explained by differences in exposure, especially given the gender ratio in hospital healthcare providers.

However, most SARS cases reported so far have been in previously healthy adults 25 to 70 years of age, and few SARS cases have been reported in children younger than 15 years of age [2]. In a prospective study of the first 10 children with SARS managed by their group in Hong Kong, Hon and colleagues found that all the children had been in close contact with infected adults, and all the children had persistent fever, cough, progressive changes in chest x-rays, and lymphopenia [10]. Although the four adolescents required oxygen therapy and two required mechanical ventilation, none of the six younger children required supplemental oxygen. Thus, SARS may have a less aggressive course in younger children. Notably, although 8 of the 10 children were attending school at the time of presentation, there was no evidence that they had transmitted the infection to any classmate.

The overall mortality rate of people with probable SARS seems to be about 4% to 6% (range, 2% to 10%), but the vast majority of deaths have been in people 50 years of age or older and/or in patients with substantial comorbidity [2]. Moreover, like other respiratory viruses, the SARS virus may also cause asymptomatic or mildly symptomatic infections that are unrecognized given the current case surveillance definitions of suspected or probable SARS. Once a “gold-standard” laboratory test is established, the range of SARS virus-related illnesses will be easier to establish.

## Diagnosis

### History

**In a patient who presents with acute onset of fever; dry cough, shortness of breath, or dyspnea; and no upper respiratory tract symptoms, consider SARS and specifically ask about recent travel or exposure to a person with similar symptoms or suspected SARS [Table 2].**

At present the case surveillance diagnosis of suspected or probable SARS requires epidemiologic data (travel from an area with known SARS in the community or close contact with a person with suspected SARS within 10 days). The onset of SARS usually consists of fever and nonspecific systemic symptoms (malaise, myalgias, chills), followed by lower respiratory tract symptoms 2 or more days later [Table 2]. Notable upper respiratory tract symptoms are uncommon, and the fever may abate with onset of lower respiratory tract symptoms (dry cough, shortness of breath, difficulty breathing). However, if or when infection with the SARS virus spreads beyond the tight epidemiologic clusters that have characterized its transmission so far, clinical differentiation of SARS, especially in the early stages, from other common winter-time respiratory tract infections will be much more difficult [11]. The constellation of symptoms and signs noted above, although not definitive, may alert clinicians to the possible diagnosis of SARS.

<b>Table 2: Key Findings from History and Physical Examination for Patients with Probable SARS</b>		
<b>Finding</b>	<b>Frequency <sup>a</sup></b>	<b>Comments</b>
<b>History</b>		
Fever	99% to 100%	Higher than 38°C (higher than 100.4°F) for more than 24 hours at presentation; may decrease before onset of respiratory symptoms and/or before presentation
Chills/rigor	78%	Common at onset
Dry cough	61%	Often starts 1 to 3 days after onset of fever
Myalgia	57%	Common at onset
Malaise	56%	Common at onset
Headache	47%	
Dizziness	34%	
Dyspnea	30%	Often starts 1 to 3 days after onset of fever
Chest pain	30%	
Sore throat	23%	
Nausea/vomiting	20%	
Diarrhea	20%	Common and severe in some cohort studies
Rhinorrhea	7%	
<b>Physical examination</b>		
Fever (higher than 37.8°C [higher than 100°F])	Common	However, a patient may be normothermic or hypothermic at presentation Lower than 35°C (lower than 95°F) or higher than 40°C (higher than 104°F) <sup>c</sup>
Tachycardia (more than 100 beats per minute)	Common <sup>b</sup>	More than 124 beats per minute <sup>c</sup>
Tachypnea (more than 20 breaths per minute)	Common <sup>b</sup>	More than 29 breaths per minute <sup>c</sup>
Borderline hypotension	Common <sup>b</sup>	Lower than 90 mmHg systolic <sup>c</sup>
Crackles/rales	Common <sup>b</sup>	Typically, inspiratory crackles at lung bases symmetrically or asymmetrically
Bronchial breath sounds, decreased air entry, or egophony	Common <sup>b</sup>	However, wheezing is rare
Other	Essentially none	Rash, lymphadenopathy, or abnormal cardiovascular, abdominal, or neurological findings are absent, unless secondary to comorbidity Altered mental status <sup>c</sup>

<b>a</b> Approximate frequency based on a composite of studies that included a total of more than 200 patients with probable SARS
<b>b</b> Based on limited data (often not assessed or reported) or wide variation in prevalence among different studies
<b>c</b> High risk factor for 30-day mortality in patients with community-acquired pneumonia in general; relevance to SARS unknown
Data from Lancet. 2003;361:1319-25. Emerg Infect Dis [serial online]. Jun 2003. <a href="http://content.nejm.org/cgi/content/abstract/NEJMoa030685v2">http://content.nejm.org/cgi/content/abstract/NEJMoa030685v2</a> . <a href="http://content.nejm.org/cgi/content/abstract/NEJMoa030634v3">http://content.nejm.org/cgi/content/abstract/NEJMoa030634v3</a> . <a href="http://content.nejm.org/cgi/content/abstract/NEJMoa030666v3">http://content.nejm.org/cgi/content/abstract/NEJMoa030666v3</a> .

### Physical Examination

**Do a general physical examination and note vital signs; expect many patients with SARS to have one or more abnormal vital sign (fever, tachycardia, tachypnea), only subtle findings on chest auscultation, and an otherwise unremarkable examination [Table 2].**

The prevalence of abnormal findings on physical examination varies considerably among the clinical studies reported so far [Table 2]. Some small studies have reported that many or most SARS patients have at least one abnormal vital sign in addition to fever on presentation, whereas other studies have not commented on vital signs other than fever [4][6][12][13][14]. However, essentially all the clinical studies have noted that in the absence of comorbidity, abnormal signs other than vital signs or chest findings are unexpected.

**Examine the chest closely for asymmetric expansion, dullness to percussion, localized differences in tactile fremitus, bronchial breath sounds, and crackles (rales), but expect most SARS patients to have minimal or no abnormal findings.**

In patients with "typical" pneumonia syndrome with pulmonary consolidation, the characteristic chest examination findings include asymmetric expansion of the chest wall, dullness to percussion, localized changes in tactile fremitus, tubular or bronchial breath sounds, and coarse (pan-inspiratory) crackles (rales) [15]. However, nonspecific signs such as crackles and wheezes can also be associated with congestive heart failure, bronchitis, or asthma, and even in patients with lobar pneumonia, specific signs of pulmonary consolidation are often not present initially.

Patients with "atypical" pneumonia, including SARS patients, are even less likely than patients with "typical" pneumonia to have consistent specific findings on chest examination [Table 2]. Some clinical series have noted that most probable SARS patients have abnormal chest auscultatory findings, whereas a large series noted that only 38% of patients had any auscultatory abnormalities on initial examination [9]. Indeed, a potential clue to SARS is consolidation on chest x-ray despite minimal auscultatory findings.

## Testing

### Office and Laboratory

**In a patient with probable SARS, consider obtaining a CBC, platelet count, creatinine phosphokinase (CPK), liver function (enzyme) tests (LFTs), urea, electrolytes, and C reactive protein (CRP) [Table 3]. Also consider chest x-ray; pulse oximetry; blood cultures; sputum Gram stain and culture; and testing for influenza A and B and respiratory syncytial virus.**

Because a specific standardized test for the SARS virus is not yet available, the WHO recommends obtaining the following tests in a patient with probable SARS: a CBC, platelet count, CPK, LFTs, urea, electrolytes, and CRP [Table 3].

Although the findings are not specific, lymphopenia, leukopenia, thrombocytopenia, and increased serum aminotransferases and CPK levels can be a clue to SARS, because this constellation of abnormalities would be unexpected in a patient with typical community-acquired pneumonia (CAP) [11].

The CDC recommends the following initial diagnostic testing: chest x-ray, pulse oximetry, blood cultures, sputum Gram stain and culture, and testing for influenza A and B and respiratory syncytial virus.

**Report cases of suspected or probable SARS to the appropriate health department, and ask about specific testing (serologic, reverse transcription polymerase chain reaction [RT-PCR], culture) for SARS virus.**

As of early May 2003 in the US, specific tests for SARS virus were not available outside a research setting. However, specific serologic antibody tests for SARS virus (indirect fluorescence antibody or enzyme-linked immunosorbent assays) that can detect SARS virus antibodies as early as 14 days after fever onset are being evaluated at the CDC and other laboratories [16][17]. Definitive interpretation of negative serologic tests requires the collection of a blood specimen more than 21 days after the onset of fever. Thus, for patients in the US with suspected SARS, a blood sample collected more than 21 days after fever onset is required to determine whether a SARS virus infection can be documented.

An RT-PCR test specific for SARS virus RNA can detect the virus in various specimens within 10 days of fever onset, but the duration of viremia and virus shedding is unknown. Viral culture followed by RT-PCR may also be used to detect SARS virus in some types of specimens.

<b>Table 3: Tests for Patients with Suspected or Probable SARS</b>		
<b>Test</b>	<b>Indications</b>	<b>Interpretation<sup>a</sup></b>
<b>Laboratory</b>		
CBC with differential	Suspected or probable SARS	Probable SARS: 20% have anemia (hemoglobin less than 11.5 g/dL) 30% have leukopenia (total white-cell count less than $3.5 \times 10^9$ cells/L) 70% have lymphopenia (less than $1 \times 10^9$ cells/L)
Platelet count	Probable SARS	40% have thrombocytopenia (less than $150 \times 10^9$ cells/L)
CPK	Probable SARS	40% have an increased CPK (more than 138 units/L)
ALT	Probable SARS	30% have an increased ALT (more than 45 units/L or more than 1.5 times the upper limit of normal; laboratory specific)
D-dimer	Probable SARS	50% have an increased level
Electrolytes	Probable SARS	20% have hyponatremia 20% have hypokalemia
Lactate dehydrogenase	Probable SARS	60% have an increased level (more than 500 units/L)
<b>Radiologic/Imaging</b>		
Chest x-ray	Suspected or probable SARS	If positive, diagnosis of suspected SARS changed to probable SARS
High-resolution CT	Suspected or probable SARS with negative chest x-ray	Otherwise not indicated If positive, diagnosis of suspected SARS changed to probable SARS
<b>Invasive</b>		
Bronchoscopy, lung biopsy	Unusual cases, special circumstances	Done by a pulmonologist, thoracic surgeon, or other endoscopist in complex cases
<sup>a</sup> Approximate values rounded to nearest decile; reported tests and some test results have varied over a wide range among studies.		
ALT, alanine aminotransferase; CBC, complete blood count; CPK, creatinine phosphokinase; CT, computed tomography; dL, deciliter; g, gram; L, liter.		
Data from <i>Lancet</i> . 2003;361:1319-25. <i>Emerg Infect Dis</i> [serial online]. Jun 2003. <a href="http://content.nejm.org/cgi/content/abstract/NEJMoa030685v2">http://content.nejm.org/cgi/content/abstract/NEJMoa030685v2</a> <a href="http://content.nejm.org/cgi/content/abstract/NEJMoa030634v3">http://content.nejm.org/cgi/content/abstract/NEJMoa030634v3</a> <a href="http://content.nejm.org/cgi/content/abstract/NEJMoa030666v3">http://content.nejm.org/cgi/content/abstract/NEJMoa030666v3</a>		

**In a patient with probable SARS, obtain specimens to exclude other treatable causes of CAP: two blood cultures, a cold-agglutinin test, a *Mycoplasma pneumoniae* immunoglobulin M titer, a *Legionella* urine antigen test, pleural fluid analysis (if present), and HIV serology [Table 4].**

Standard tests that help to exclude other potentially treatable causes of CAP, in addition to a CBC and chest x-ray, include at least two blood cultures, a cold-agglutinin test, a *M. pneumoniae* immunoglobulin M titer, a *Legionella* test (urine antigen), pleural fluid analysis (if present), and HIV serology (if the patient is 15 to 54 years of age with otherwise unexplained lymphocytopenia). Also, consider other tests based on specific patient indications [Table 4]. The CDC recommends obtaining specific specimens to evaluate SARS based on the patient's status [Table 5].

<b>Table 4: Potential Tests for Microbial Diagnosis of Community-Acquired Pneumonia</b>		
<b>Test</b>	<b>Comments</b>	<b>Possible Indications</b>
<b>Noninvasive</b>		
Sputum Gram stain	Conceptually, very helpful; practically, requires optimal specimen collection and processing, and expert interpretation	Most appropriate in patients with severe CAP, failure to respond to initial antibiotics, or immune deficiency
Sputum cultures	Diagnostic yield, 20% to 79%; overgrowth of oral flora problematic; isolation of atypical agents requires special media	Same as above
Blood culture	Even when obtained before antibiotics are initiated, the diagnostic yield is only 5% to 16%; however, specificity is high	All hospitalized patients with pneumonia
Antigen studies	At present the only practical expedient test is the urine antigen for <i>Legionella pneumophila</i> type 1, which has a sensitivity of 70% and a specificity of 100%	Although <i>Legionella</i> is uncommon, it accounts for 12% to 23% of cases of severe CAP; thus, testing is indicated in patients with severe CAP or risk factors for <i>Legionella</i> pneumonia
Serologic studies	Generally require 4-fold increase in titer, which takes too long for practical clinical management	Consider for sicker patients with a protracted course or failed initial treatment; specific immunoglobulin M for <i>Mycoplasma pneumoniae</i> may be useful earlier
PCR	Potentially the ideal test for CAP, but at present practical	Indicated on specimen smears that are positive for acid-fast

	only for Mycobacterium tuberculosis; however, a standardized RT-PCR test for SARS virus may soon be available	bacilli; for patients with probable SARS, contact your state or local public health department about RT-PCR availability and specimen collection and transport
<b>Invasive tests</b> (to obtain specimens for microbiological and/or histopathologic studies)		
Thoracentesis	Most common invasive procedure; sensitivity is low because most parapneumonic effusions are sterile, but specificity is high	Indicated for patients with significant pleural effusion (10 cm or larger on a lateral decubitus x-ray); however, pleural effusion rarely if ever associated with SARS
Fiberoptic bronchoscopy	Most appropriate in intubated, mechanically ventilated patients; diagnostic yield improved by using protected brush or BAL	These invasive procedures are reserved for the sickest patients with typical or atypical pneumonia, particularly those who are immunocompromised, have failed treatment, and/or have a suspected noninfectious process In suspected or probable SARS patients, particularly strict infection control measures are indicated to prevent transmission of infection to operator or nearby healthcare staff
Transthoracic needle aspiration	Use of thin needles reduces complication rates (pneumothorax, less than 10%; hemoptysis, 5% or less)	
Transtracheal aspiration	Diagnostic sensitivity and specificity are moderately high, but potential complications limit use	
Thoracoscopic lung biopsy	Potentially a less invasive alternative to open-lung biopsy	
Open-lung biopsy	Provides best specimens, but only used if less invasive studies fail	
<b>BAL, bronchoalveolar lavage; CAP, community-acquired pneumonia; cm, centimeter; RT-PCR, reverse transcription polymerase chain reaction.</b>		
<b>Data from <i>Infect Dis Clin Pract.</i> 1996;5:147-67; <i>Clin Infect Dis.</i> 2000;31:247-82; <i>Clin Infect Dis</i> 2000;31:383-421.</b>		

<b>Table 5: Specimens for Evaluating Potential Cases of SARS</b>	
<b>Source</b>	<b>Comment</b>
<b>Outpatient</b>	
Upper respiratory	Nasopharyngeal and oropharyngeal swabs
Blood	Serum: acute and convalescent
	Whole blood
Stool	
<b>Inpatient</b>	
Upper respiratory	Nasopharyngeal aspirate
	Nasopharyngeal and oropharyngeal swabs
Lower respiratory	Bronchoalveolar lavage; tracheal aspirate; pleural tap
Blood	Serum: acute and convalescent
	Whole blood
Stool	
<b>Fatal</b>	
Tissue	Fixed tissue from all major organs (lung, heart, spleen, liver, brain, kidney, adrenals)
	Frozen tissue from lung and upper airway (trachea, bronchus)
Upper respiratory	Nasopharyngeal aspirate
	Nasopharyngeal and oropharyngeal swabs
Lower respiratory	Bronchoalveolar lavage; tracheal aspirate; pleural tap
Blood	Serum
	Whole blood
Stool	
<b>Data from <a href="http://www.cdc.gov/ncidod/sars/specimen_collection_sars2.htm">http://www.cdc.gov/ncidod/sars/specimen_collection_sars2.htm</a></b>	

### **Radiologic**

**Obtain at least a posterior-anterior chest x-ray in patients at risk for SARS (those with fever and potential SARS exposure within the preceding 10 days), with or without lower respiratory tract symptoms or signs [Table 3].**

Most otherwise healthy patients with acute symptoms of lower respiratory tract infection but no known epidemiologic risk factors for SARS have acute bronchitis, so a chest x-ray is generally not warranted unless they have at least two of the following signs: temperature higher than 37.8°C (100°F); pulse rate more than 100 beats per minute; respiratory rate higher than 20 breaths per minute; decreased breath sounds; and crackles/rales.

However, note that most patients with SARS have an abnormal chest x-ray at presentation, whether or not they have lower respiratory tract symptoms or signs. In a study of 138 hospitalized patients with probable SARS, 78% had an abnormal chest x-ray at presentation [4]. All of the abnormal chest x-rays showed air-space consolidation, with unifocal involvement in 55%, and either unilateral

multifocal or bilateral involvement in 45%. Notably, peripheral involvement is predominant, and the findings are indistinguishable from those of other causes of bronchopneumonia. However, the absence of pleural effusion, calcification, cavitation, or hilar adenopathy in SARS patients helps limit the diagnostic possibilities.

Early in the disease, the only abnormality may be a peripheral, pleural-based, ground-glass to consolidated opacity [18]. It is important to focus on the paraspinal area behind the heart; high-resolution CT often detects lesions in that area that were missed on plain-film chest x-rays. Advanced disease is typically associated with widespread opacification that affects the lower zones first and tends to be bilateral.

An initial chest x-ray can establish the presence of infiltrate(s), serve as a baseline for serial chest x-ray monitoring of progression, and rule out other causes of respiratory compromise, such as pulmonary cavitation or abscess, pneumothorax, lymphadenopathy, or tumor-related bronchial obstruction.

**If a patient with suspected SARS has a negative chest x-ray, consider obtaining high-resolution CT (HRCT) of the thorax [Table 3].**

If the chest x-ray is abnormal (for example, shows a new infiltrate), then no further imaging is required, other than follow-up serial x-rays. However, if the chest x-ray is normal, HRCT is indicated. Although standard chest CT is useful for detecting interstitial lung disease, bronchiolitis obliterans, empyema, cavitation, hilar adenopathy, or multifocal disease, HRCT is the imaging study of choice for detecting SARS-associated infiltrates [18].

HRCT may reveal changes 1 to 2 days before such abnormalities are apparent on chest x-rays. However, because HRCT may result in over-diagnosis, obtain HRCT only if the chest x-ray is normal and there is either a history of SARS contact or clinical manifestations (persistent fever, lymphopenia, and so on) that are strongly indicative of SARS [18].

### **Invasive**

**In general, consider invasive procedures, such as fiberoptic bronchoscopy with bronchoalveolar lavage (with or without transbronchial biopsy), only to evaluate patients with probable SARS if they have progressive deterioration and fail to respond to therapy and you suspect serious treatable comorbidity or an alternative diagnosis [Table 3][Table 4].**

Fiberoptic bronchoscopy with bronchoalveolar lavage is usually reserved for the diagnosis of rapidly progressive pneumonia in an immunocompromised patient, or in a patient with “enigmatic,” chronic, or progressive pneumonia [Table 3][Table 4][19]. Quantitative culture of bronchoalveolar lavage specimens improves the specificity of microbial isolates, and transbronchial biopsy can be

helpful in diagnosing viral, fungal, and neoplastic disease. Some studies have indicated that SARS patients have large viral loads in their saliva and respiratory secretions, so such patients should generally not require an invasive diagnostic procedure in the absence of suspected serious co-infection or an alternative diagnosis [9].

### **Differential Diagnosis**

**Consider the diagnosis of SARS in a patient who presents with fever, with or without lower respiratory tract symptoms, and a history of potential exposure to SARS within the last 10 days; otherwise, keep SARS in mind, but assess the patient for more likely diseases, such as acute bronchitis or community-acquired pneumonia (CAP) unrelated to SARS virus [Table 6].**

Unlike typical SARS patients, most patients with acute bronchitis report an acute onset of coughing associated with sputum production and symptoms of an upper respiratory illness, and little or no fever [Table 6]. However, as in typical SARS patients, the chest examination findings are usually nonspecific, such as scattered rhonchus sounds, wheezing (rare with SARS), and/or rales (crackles). The findings are typically transient (may or may not clear after coughing) and lack apparent focal involvement or consolidation.

**Suspect CAP in a patient who presents with an acute onset of fever (or hypothermia), cough (dry or productive), dyspnea, and/or chest discomfort, and who on physical examination has tachypnea (more than 25 breaths per minute), bronchial breath sounds, and/or rales [Table 6].**

If the patient has dyspnea, tachypnea, high fever (above 38.8°C or 102°F), or persistent focal lung findings, and/or seems toxic or distressed, obtain chest x-rays (posteroanterior and lateral) to identify or exclude CAP [Table 6]. However, patients with no known exposure to SARS, normal vital signs, and no focal lung findings on physical examination do not require chest x-rays (see related information on community-acquired pneumonia and acute bronchitis).

To maintain perspective, physicians practicing in the US should consider that about 4 million people in the US experience CAP annually, about 600,000 are hospitalized with CAP, and about 12% to 14% of those hospitalized with CAP die [20]. In contrast, as of early May 2003, only about 50 patients in the US had been diagnosed with probable SARS, and none had died. Thus, in the absence of a history of potential exposure to SARS, a patient presenting to a physician in the US, or in other non-Asian countries, is far more likely to have pneumonia due to a cause other than SARS.

<b>Clinical findings</b>	<b>Diagnosis to consider</b>	<b>Test results/comments</b>
Acute onset of fever with systemic symptoms; onset of lower respiratory symptoms 2 to 7 days later; history of potential SARS exposure within 10 days	SARS	Except for fever, the general and chest examination are often unremarkable, but most patients have one or more infiltrates on chest x-ray
Acute lower respiratory illness starting outside of a hospital; fever	Community-acquired pneumonia	Persistent, localized bronchial breath sounds or rales Parenchymal infiltrate(s) on chest x-ray
Acute onset with prominent cough and systemic symptoms during known epidemic	Influenza	Leukopenia Chest x-ray usually normal Positive PCR or rapid immunologic test Clinical diagnosis about 70% accurate during an epidemic
Wheezing and dyspnea; usually in afebrile patient with known asthma or atopy	Asthma; transient reversible airways disease	Prolonged expiration and diffuse wheezing Spirometry shows airflow obstruction Chest x-ray shows hyperinflation only Uncomplicated acute bronchitis can cause transient bronchial hyperresponsiveness
High risk for tuberculosis; possible cough, fatigue, weight loss, fever, and/or night sweats	Tuberculosis	Chest x-ray typically shows apical infiltrates PPD test usually positive Positive sputum smear for acid-fast bacilli and positive culture for <i>Mycobacterium tuberculosis</i>
<b>PCR, polymerase chain reaction; PPD, purified protein derivative.</b>		

## Diagnostic Criteria

**Diagnose suspected SARS in a patient who meets the CDC clinical criteria for idiopathic moderate respiratory illness (temperature above 38°C [100.4°F] plus cough, dyspnea, or hypoxia) and CDC epidemiologic criteria (onset within 10 days of potential exposure).**

Although the interim US surveillance cases definition for suspected SARS is recommended for reporting and classification purposes only, not clinical management, it serves as a guide to the clinical diagnosis [3]. If possible, clinicians should document the temperature, but may use clinical judgment (history of fever, antipyretic use) when assessing this criterion. A suspected SARS classification requires that the patient satisfy the clinical criteria for moderate respiratory illness of unknown etiology with onset since February 1, 2003, and the epidemiologic criteria. The moderate respiratory illness criteria include a temperature above 38°C (100.4°F) and one or more clinical findings of respiratory illness (cough, shortness of breath, difficulty breathing, or hypoxia). The epidemiologic criteria include either travel within 10 days of symptom onset to an area with documented or suspected community transmission of SARS or close contact within 10 days of symptom onset with a person known to be a suspected SARS case. Laboratory criteria (confirmed, negative, undetermined) are now included with the US surveillance case definition but are not yet used to modify the case classification.

**Diagnose probable SARS in a patient who meets the CDC criteria for suspected SARS and has at least one of the following: x-ray evidence of pneumonia, (acute) respiratory distress syndrome, or compatible autopsy findings.**

A WHO classification of probable SARS requires that the patient satisfy the clinical criteria for severe respiratory illness of unknown etiology with onset since February 1, 2003, and the same epidemiologic criteria as the CDC criteria for suspected SARS [3]. The moderate respiratory illness criteria include a temperature above 38°C (100.4°F), at least one clinical finding of respiratory illness (cough, shortness of breath, difficulty breathing, or hypoxia), and radiographic evidence of pneumonia or respiratory distress syndrome, or autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause.

In the US, patients with suspected SARS are reported to the CDC and WHO, whereas only patients with probable SARS are reported to the WHO from other countries. Again, laboratory criteria (confirmed, negative, undetermined) are now included with the US CDC surveillance case definition but are not yet used to modify the case classification.

## Treatment

### Acute Care/Hospitalization

**For patients with suspected SARS, consider following the WHO recommendations of immediate triage, surgical mask use, detailed history (travel, contacts), CBC, chest x-ray, and hospitalization of patients with unilateral or bilateral infiltrates on chest x-ray.**

The WHO recommendations for management of patients with suspected SARS include:

- Immediately triage to designated examination room or ward
- Provide patient with a surgical mask
- Obtain and record detailed clinical, travel, and contact history, including symptoms of acute respiratory disease in contacts during the preceding 10 days
- Obtain a chest x-ray and CBC
- If the chest x-ray is normal, advise the patient about personal hygiene, and instruct the patient to avoid crowded areas and public transportation, to remain at home until well, and to seek medical care if respiratory symptoms worsen
- If the chest x-ray shows unilateral or bilateral infiltrates, with or without interstitial infiltration, change the diagnosis to probable SARS and hospitalize the patient

**For patients with probable SARS, consider following the WHO recommendations: hospitalize under isolation; exclude other causes of pneumonia; obtain a CBC, platelet count, creatinine phosphokinase (CPK), liver tests (LFTs), urea, electrolytes, and C-reactive protein (CRP); and initiate antibiotics to cover typical and atypical causes of community-acquired pneumonia (CAP) [Table 7]**

**[\(www.who.int/csr/sars/management/en/\)](http://www.who.int/csr/sars/management/en/).**

The WHO recommendations for management of patients with probable SARS include:

- Hospitalize under isolation or cohort with other probable SARS patients
- Obtain laboratory samples to exclude other causes of typical and atypical pneumonia [Table 4]
- Obtain a CBC, platelet count, CPK, LFTs, urea, electrolytes, and CRP [Table 3]
- Initiate antibiotic coverage for both typical and atypical CAP [Table 7]
- Use appropriate infection-control precautions during procedures that cause aerosolization (nebulization, chest physiotherapy)

- Note that antibiotics and ribavirin, with or without corticosteroids, are of unproven benefit; thus, strongly consider obtaining an infectious disease consultation and reviewing the latest guidelines when managing SARS patients

**For hospitalized patients suspected of having SARS, consider following the CDC recommendations of immediately notifying control personnel, and using hand hygiene, eye protection, gowns and gloves, negative pressure isolation rooms, and N-95 filtering disposable respirators for visitors.**

The CDC recommendations for hospitalized patients with suspected SARS include:

- Immediate notification of infection-control personnel
- Hand hygiene
- Eye protection
- Gown and gloves
- Negative pressure isolation room
- N-95 filtering disposable respirator for people entering the room

If airborne precautions cannot be fully implemented, patients should be placed in a private room, and all people entering the room should wear N-95 respirators.

<b>Table 7: Empirical Antimicrobials for Hospitalized Adults with Community-Acquired Pneumonia<sup>a</sup></b>			
<b>Patient characteristics</b>	<b>First choice</b>	<b>Second choice</b>	<b>Typical pathogens</b>
On medical ward	Respiratory fluoroquinolone <sup>c</sup>	2 <sup>nd</sup> to 4 <sup>th</sup> G cephalosporin <sup>d</sup> plus macrolide <sup>b</sup>	<i>S. pneumoniae</i> , <i>M. pneumoniae</i> , and <i>C. pneumoniae</i>
In ICU	Intravenous respiratory fluoroquinolone <sup>c</sup> plus cefotaxime, ceftriaxone or beta-lactam/beta-lactamase inhibitor <sup>e</sup>	Intravenous macrolide plus cefotaxime, ceftriaxone or beta-lactam/beta-lactamase inhibitor <sup>e</sup>	<i>S. pneumoniae</i> , <i>L. pneumophila</i> , <i>C. pneumoniae</i> , enteric Gram-negative rods
In ICU (severe structural lung disease, or recently completed course of antibiotics or corticosteroids)	Antipseudomonal fluoroquinolone (ciprofloxacin) plus antipseudomonal beta-lactam <sup>f</sup> or aminoglycoside <sup>g</sup>	Triple therapy with antipseudomonal beta-lactam <sup>f</sup> plus aminoglycoside <sup>g</sup> plus macrolide	<i>P. aeruginosa</i>
<sup>a</sup> <b>Main pathogens: <i>Streptococcus pneumoniae</i>, <i>Mycoplasma pneumoniae</i>, <i>Chlamydia pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>Legionella pneumophila</i>, <i>Pseudomonas aeruginosa</i></b>			
<sup>b</sup> <b>Erythromycin, azithromycin, clarithromycin</b>			
<sup>c</sup> <b>Levofloxacin, gatifloxacin, moxifloxacin</b>			
<sup>d</sup> <b>2nd-G (generation) cephalosporins: cefuroxime, cefprozil; 3rd-G, cefotaxime, ceftriaxone; 4th-G, cefepime</b>			
<sup>e</sup> <b>Beta-lactam/beta-lactamase inhibitor: piperacillin/tazobactam</b>			
<sup>f</sup> <b>Antipseudomonal beta-lactam: ceftazidime, piperacillin/tazobactam, imipenem, meropenem</b>			
<sup>g</sup> <b>Gentamicin, amikacin, tobramycin)</b>			
<b>COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.</b>			
<b>Data from <i>Clin Infect Dis.</i> 2000;31:247-82.</b>			

**Admit SARS patients to the intensive care unit (ICU) if they require mechanical ventilation for respiratory failure (evidenced by breathing rate of more than 35 breaths per minute, arterial oxygen pressure of less than 90% on 50% supplemental oxygen, systolic blood pressure of less than 90 mmHg) or for hemodynamic support and close monitoring.**

Essentially all previously healthy patients with SARS who are admitted to an ICU are in respiratory failure and usually require mechanical ventilation [4]. Typical manifestations of respiratory that predict the need for mechanical ventilation include tachypnea (more than 31 to 35 breaths per minute), arterial hypoxemia despite oxygen supplementation (for example, an arterial oxygen pressure of less than 90% on 50% supplemental oxygen), and shock (systolic blood pressure of less than 90 mmHg or diastolic blood pressure of less than 60 mmHg) [20].

### Lifestyle Measures

**Until 10 days after fever and respiratory symptoms have disappeared, advise outpatients with suspected SARS to continue infection-control precautions, including limiting social interactions, practicing regular hand hygiene, wearing a surgical mask, and frequently using household cleaners ([www.cdc.gov/ncidod/sars/ic-closecontacts.htm](http://www.cdc.gov/ncidod/sars/ic-closecontacts.htm)).**

Basic infection-control precautions in the household for suspected SARS patients include:

- Until 10 days after fever and respiratory symptoms are gone, SARS patients should limit social interactions outside the home and not go to school, work, out-of-home care, or other public areas.
- All household members should carefully follow recommendations for hand hygiene, such as frequent washing or use of alcohol-based hand rubs.
- Before sneezing or coughing, SARS patients should cover their nose and mouth with a tissue. If possible, SARS patients should wear a surgical mask when in close contact with uninfected people; otherwise, uninfected people should wear one when in contact with SARS patients.
- Wear disposable “surgical” gloves for any contact with body fluids from a SARS patient. Moreover, immediately after contact with body fluids, discard the gloves and wash your hands. Gloves do not replace hand washing, and do not wash or reuse gloves.
- SARS patients should not share eating utensils, towels, or bedding with household members; however, the items have been washed or laundered with soap and water, household members may use them.
- With frequent use, common household cleaners are sufficient for disinfecting sinks, toilets, and other surfaces touched by SARS patients.
- Unless they develop fever or respiratory symptoms, other household members need not restrict outside activities.

### Medical Therapy

**In patients with severe and progressive SARS, consider empirical treatment with intravenous ribavirin and hydrocortisone, but only after reviewing the latest management guidelines and obtaining an infectious disease consultation ([www.who.int/csr/sars/management/en/](http://www.who.int/csr/sars/management/en/)).**

Based on theoretical considerations and personal experience, but not controlled studies, the Hospital Authority of Hong Kong recommends a protocol that includes intravenous ribavirin and intravenous hydrocortisone [Table 7], plus

antibiotic coverage for typical and atypical agents for 7 to 14 days with drugs such as levofloxacin and macrolides [1]. They also recommend anti-ulcer prophylaxis.

Ribavirin is a ribonucleoside analog that has broad-spectrum activity against RNA viruses, including a pneumovirus related to human metapneumoviruses and coronaviruses [13][21]. Although empirical treatment of acute respiratory distress syndrome (ARDS) with ribavirin may be reasonable until further information is available, neither the WHO nor the CDC recommends ribavirin, or any antiviral agent, as the standard of care at this time.

Most of the patients with probable SARS in the US have not been treated with specific antiviral therapy, and all have recovered or clinically stabilized. Ribavirin is a known teratogen with many potential adverse effects, including severe hemolytic anemia [17]. Preliminary in vitro test results indicate that ribavirin concentrations that inhibit other ribavirin-sensitive viruses do not inhibit cell-to-cell spread or replication of SARS virus.

Because both the high prevalence of abnormal laboratory findings (severe lymphopenia, increased liver enzymes, thrombocytopenia) and the progression into ARDS indicate severe systemic inflammatory injury, immunomodulation by corticosteroid therapy to complement ribavirin therapy is advocated by various authorities [4][6]. However, whether corticosteroid therapy benefits patients with either SARS or ARDS is unclear.

<b>Selection criteria</b>	<b>Drugs and dosages</b>	<b>Prescribing highlights</b>
Consider for probable SARS patient with severe, progressive disease, after infectious disease consultation	<b>Ribavirin (Rebetol)</b> 8 mg/kg every 8 hours intravenously, or 1.2 g every 12 hours orally for 7 to 14 days	Combined therapy with both ribavirin and hydrocortisone
	<b>Hydrocortisone</b> 2 mg/kg every 6 hours intravenously or 4 mg/kg every 8 hours intravenously; when there is obvious clinical improvement, taper and stop over 1 week	Start oral ribavirin treatment with a loading dose of 4 g if the patient has normal renal function  In rapidly deteriorating severe cases, initiate corticosteroid therapy with methylprednisolone, followed by hydrocortisone
	<b>Methylprednisolone (Solu-Medrol)</b> 10 mg/kg every 24 hours intravenously for 2 days, followed by hydrocortisone as above	Monitor the hemoglobin concentration, reticulocyte count, and blood glucose and potassium levels
<b>g, gram; kg, kilogram; mg, milligram.</b>		

**Consider hospital discharge in a convalescent SARS patient with no fever for 48 hours, resolving cough, normalized laboratory studies, and chest x-ray changes showing improvement.**

The WHO advises that the above criteria be met before a decision is made about hospital discharge of a convalescent patient with SARS [15].

### **Invasive Procedures**

**Intubate and mechanically ventilate SARS patients with respiratory failure who do not adequately respond to noninvasive supplemental oxygen and respiratory support measures.**

Typical SARS patients who require mechanical ventilation meet the diagnosis criteria for adult respiratory distress syndrome (ARDS), which include diffuse infiltrates on chest x-ray and hypoxemia without evidence of left ventricular heart failure [13]. Therapy for ARDS is supportive; mechanical ventilation is used to improve oxygenation and to decrease the work of breathing [22]. The optimal approach for ventilating patients with SARS is unknown, but it seems reasonable to follow the lung-protection strategy (ventilation with low tidal volumes) that reduces the mortality of patients with ARDS [13][23].

## Complications

**Be aware that respiratory failure is the main complication of SARS; these patients will require intubation and mechanical ventilation when they fail to adequately respond to noninvasive supplemental oxygen and respiratory support measures.**

Respiratory failure is the main potential complication of SARS. In a series of 138 hospitalized patients with probable SARS, 32 (23%) were admitted to the intensive care unit (ICU), all for respiratory failure, and 19 (14%) required mechanical ventilatory support with positive end-expiratory pressure [4]. All 32 patients who required ICU admission had substantial increases in shortness of breath, hypoxemia, and increases in lung opacity at a median of 6.5 days (range, 3 to 12 days) that led to their ICU admission. Of the 19 patients who required mechanical ventilatory support, 5 died; all 5 who died had originally been admitted because of other major medical disorders.

## Special Circumstances

**If applicable, review recent CDC and WHO information about avoiding SARS transmission in special settings**

**([www.cdc.gov/ncidod/sars/exposureguidance.htm](http://www.cdc.gov/ncidod/sars/exposureguidance.htm)) or related to travel ([www.cdc.gov/travel/other/acute\\_resp\\_syn\\_multi.htm](http://www.cdc.gov/travel/other/acute_resp_syn_multi.htm)).**

Also, close contacts of SARS patients should be screened for fever or respiratory symptoms before visiting a healthcare facility and should not be allowed to enter the facility if they have fever or respiratory symptoms

([www.cdc.gov/ncidod/sars/infectioncontrol.htm](http://www.cdc.gov/ncidod/sars/infectioncontrol.htm)).

The WHO recommends pre-departure screening for SARS symptoms of airline passengers from some countries ([www.who.int/csr/sars/travel/en/](http://www.who.int/csr/sars/travel/en/)). Quarantine inspectors meet aircraft or ships reporting ill passengers or crew on arrival in the US ([www.ced.gov/ncidod/dg/pdf/42cfr71.pdf](http://www.ced.gov/ncidod/dg/pdf/42cfr71.pdf)).

## When to Consult or Refer

**Strongly consider consulting an infectious disease specialist and/or pulmonologist for all patients with probable SARS, especially before initiating potentially toxic and unproven specific antiviral (ribavirin) or corticosteroid therapy.**

Generally, patients with suspected SARS are managed as outpatients and do not routinely require consultation, unless their management is problematic. In contrast, patients who have probable SARS should be hospitalized and isolated, because they are at much higher risk for transmission of infection and for rapid progression to respiratory failure. Because of the rapid changes and advances in the diagnosis and treatment of SARS patients, and the absence of controlled trials to guide management, help from a specialist with practical experience

managing SARS patients and/or patients with pneumonia and respiratory failure is potentially invaluable.

### Prognosis

**Among patients hospitalized with probable SARS, consider the risk factors for intensive care unit (ICU) admission and/or death to include major comorbidity, advanced age, male gender, a high peak creatinine kinase level, a high lactate dehydrogenase (LDH) value, and a high absolute neutrophil count.**

In a study of 138 patients with probable SARS, 23% were admitted to the ICU, and 3.6% (5 patients) died [4]. On univariate analysis, advanced age, male gender, a high peak creatine kinase value, a high LDH level on presentation and a high peak value, a high absolute neutrophil count on presentation, and a low serum sodium level were highly predictive factors for ICU admission and death. On multivariate analysis, the only negative predictive factors were advanced age, a high peak LDH level, and an increased absolute neutrophil count on presentation. Probably because of the low number of patients, comorbidity was not statistically associated a poor prognosis; however, all 5 of the patients who died had significant comorbidity, whereas only 19 of the 138 patients overall had significant comorbidity. Moreover, other studies have also reported that most SARS patients who die have comorbidity [6].

### Patient Education

#### General Information

**Educate patients about what is known about the natural history of SARS and SARS virus, and about control measures as indicated for the specific patient [Table 1].**

Consider either obtaining printed information for patient distribution from the CDC and WHO SARS Internet sites or referring patients who have Internet access to those sites [Table 1]. Good examples of patient materials at the CDC Internet site include “Fact Sheet: Basic Information about SARS” and “Frequently Asked Questions: Severe Acute Respiratory Syndrome (SARS).” For patient information about outpatient infection control, consider <http://www.cdc.gov/ncidod/sars/ic-closecontacts.htm>.

Also, educate patients who plan foreign travel about regularly updated WHO, CDC, and Health Canada travel advisories pertaining to visiting countries with local transmission of SARS [Table 1].

#### Follow-up

**Instruct discharged convalescent patients to measure and record their temperature twice daily; to remain at home, stay indoors, and minimize contact with others; and to return for a follow-up visit in one week.**

Advise patients that if their temperature is above 38°C (100.4°F) on two consecutive measurements to report to the healthcare facility from which they were discharged [24]. At their 1-week follow-up, they should have a chest x-ray and CBC, and should repeat any other blood tests that were previously abnormal. Subsequent confinement is usually recommended only for immunosuppressed patients. Additional follow-up visits are recommended until the patient's chest x-ray and health have normalized. At 3 weeks after disease onset, obtain a blood specimen for convalescent serology, and send the specimen to the healthcare facility from which the patient was discharged. Give patients clear instructions about what to do if their condition deteriorates or they develop any additional symptoms.

### **Prevention and Screening**

**Consider using selected procedures or questionnaires for SARS screening based on the population and risk (travelers from areas with community transmission, healthcare workers, and so on), but focus on the two essential issues: fever and potential exposure within the last 10 days.**

Especially in low-risk areas outside Asia, almost all patients with probable SARS have had a history of recent fever and either travel to an area of known community transmission of SARS or exposure to a person with suspected or probable SARS within the preceding 10 days. Various questionnaires have been developed to screen people traveling from endemic areas or healthcare workers coming to work. Examples of an evolving expedient electronic screening tool used to screen hospital workers are available at the Canadian Medical Association Journal Web site [Table 1][25].

People with suspected or probable SARS usually have systemic and respiratory symptoms, but such symptoms are nonspecific and are often caused by non-SARS-related disorders. In contrast, relatively few people in a population outside Asia will have returned from Hong Kong or China, or will have been closely exposed to a person with suspected SARS, within the past 10 days, and a fever above 38°C (100.4°F) that persists for more than 24 hours is uncommon in otherwise healthy community-dwelling adults with common infectious illnesses, unless influenza is epidemic in the community. Thus, focusing on the combination of epidemiologic criteria of the CDC and WHO (exposure within 10 days) and notable fever might be the most practical, sensitive, and specific screening test.

**Base SARS prevention on current standard infection-control recommendations from the CDC and WHO relevant to the setting (hospital or community) and on their travel advisories (avoid nonessential travel to areas with community transmission of disease).**

The CDC and WHO Internet sites include frequently updated infection control recommendations for almost all settings (home, work, hospital, cruise ship, airplane) [Table 1]. For now, prevention of SARS is based on infection control. If the natural history of SARS evolves to mimic that of influenza, then containment

will require vaccination, prophylaxis, and/or treatment [26]. At present, many known and experimental antiviral agents are undergoing in vitro testing against SARS virus, and vaccine development is underway. Because vaccines against other coronaviruses are effective in animals, there is reason to believe that an effective vaccine can be developed for humans. Meanwhile, control rests on local, national, and international cooperation in public health measures, and on consistent use of infection control measures when indicated.

### Key References

Papers of particular interest.

\*\*Lee N, Hui D, Wu A, et al: **A major outbreak of severe acute respiratory syndrome in Hong Kong.** *N Engl J Med.* 2003. Published online on 7 April 2003

Includes the clinical, laboratory, and radiologic features of 138 patients with suspected SARS during a hospital outbreak in Hong Kong, the largest series reported so far. (<http://nejm.org/earlyrelease/sars.asp>)

\*\*Peiris JSM, Lai ST, Poon LLM, et al: **Coronavirus as a possible cause of severe acute respiratory syndrome.** *Lancet.* 2003;361:1319-25.

Detailed review of the viral investigations and clinical presentations of 50 patients (<http://image.thelancet.com/extras/03art3477web.pdf>)

\*\*Ksiazek TG, Erdman D, Goldsmith CS, et al: **A novel coronavirus associated with severe acute respiratory syndrome.** *N Engl J Med.* 2003;348(20):1947-58. (published at [www.nejm.org](http://www.nejm.org) on 10 April 2003)

Describes the identification of the newly identified coronavirus in various specimens from a series of 18 patients.

\*\*Ahuja AT, Wong JKT, Griffith JF, et al: **Radiological appearances of recent cases of atypical pneumonia in Hong Kong.** (<http://www.droid.cuhk.edu.hk>)

Regularly updated Internet site that includes many high-quality examples of plain chest x-rays and corresponding high-resolution studies from SARS patients.

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### **Evidence Highlights**

At the time of the most recent revision of this document, no randomized, controlled studies or systematic reviews were found in the sources used for Evidence Highlights.

### **Drugs to Consider**

#### **Antivirals**

Ribavirin (Rebetron)

#### **Corticosteroids**

Hydrocortisone

Methylprednisolone (Solu-Medrol)

- **For more information about SARS, please see the SARS document written for patients.**
- **For more information about the DISEASEDEX™ General Medicine System, please see the DISEASEDEX™ product page at <http://www.micromedex.com/products/diseasedexgeneral/>.**