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## REVIEW ARTICLE

## CURRENT CONCEPTS

## The Severe Acute Respiratory Syndrome

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**T**HE SEVERE ACUTE RESPIRATORY SYNDROME (SARS) IS RESPONSIBLE FOR the first pandemic of the 21st century. Within months after its emergence in Guangdong Province in mainland China, it had affected more than 8000 patients and caused 774 deaths in 26 countries on five continents. It illustrated dramatically the potential of air travel and globalization for the dissemination of an emerging infectious disease and highlighted the need for a coordinated global response to contain such disease threats. We review the cause, epidemiology, and clinical features of the disease.

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## CAUSE

An unusual atypical pneumonia emerged in Foshan, Guangdong Province, mainland China, in November 2002.<sup>1,2</sup> In February and March 2003, the disease spread to Hong Kong and then to Vietnam, Singapore, Canada, and elsewhere (Table 1).<sup>3,4</sup> The new disease was named the severe acute respiratory syndrome (SARS), and a preliminary case definition was established.<sup>4</sup> A novel coronavirus (SARS-CoV) was identified as the causative agent.<sup>5-10</sup> Coronaviruses are a family of enveloped, single-stranded-RNA viruses causing disease in humans and animals, but the other known coronaviruses that affect humans cause only the common cold.

The presence of SARS-CoV has been demonstrated by reverse-transcriptase polymerase chain reaction (RT-PCR) and the isolation of the virus from respiratory secretions, feces, urine, and tissue specimens from lung biopsy,<sup>11,12</sup> indicating that the infection is not confined to the respiratory tract. The experimental infection of cynomolgus macaques with SARS-CoV produced a pneumonia that was pathologically similar to SARS in humans.<sup>8,9</sup> Other pathogens, including human metapneumovirus<sup>13,14</sup> and chlamydia,<sup>7,15</sup> have been detected together with SARS-CoV in some patients with SARS, but they have not been found consistently.<sup>5,9</sup> The experimental infection of macaques with human metapneumovirus did not lead to a SARS-like disease, and coinfection of macaques with human metapneumovirus and SARS-CoV did not enhance the pathogenicity of the SARS-CoV in this animal model.<sup>8</sup> Thus, all the information that is available to date suggests that SARS-CoV is necessary and sufficient for the causation of SARS in humans, but it remains to be determined whether microbial or other cofactors enhance the severity or transmissibility of the disease. The complete genetic sequence of the SARS-CoV genome was determined, and it provided confirmation that SARS-CoV belongs to a new group within the coronavirus family (Table 1).<sup>16,17</sup>

Since seroepidemiologic data<sup>5,6,12,18</sup> suggested that SARS-CoV had not previously been endemic in humans, it seemed likely that this was a virus of animals that had crossed the species barrier to humans in the recent past. This hypothesis was further supported by anecdotal reports that some patients who had SARS in Guangdong Province in November and December 2002 reported a history of occupational exposure to live, caged animals that are used as exotic "game food," a culinary delicacy in southern

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**Table 1. A Chronology of Events.\***

Date	Key Events
November 2002	Unusual atypical pneumonia documented in Foshan, Guangdong Province, China.
January 2003	Outbreaks of pneumonia in Guangzhou (capital city of Guangdong Province).
February 11, 2003	WHO receives reports of an outbreak of respiratory disease in Guangdong Province: 305 cases and 5 deaths.
February 20, 2003	Fatal influenza A (H5N1 subtype) identified in family returning to Hong Kong from Fujian Province, China.
February 21, 2003	65-Year-old doctor from Guangdong Province checks in at "Hotel M" in Hong Kong (index patient); he has been ill since February 15. His health deteriorates further; he is admitted to the hospital on February 22. He infects at least 17 other guests and visitors at the hotel, some of whom travel to Vietnam, Singapore, and Toronto, where they initiate transmission of local clusters of cases.
February 26, 2003	A Hotel M contact is admitted to a private hospital in Hanoi and is the source of an outbreak there; 7 health care workers become ill by March 5.
March 4, 2003	A Hotel M contact is admitted to Prince of Wales Hospital in Hong Kong. By March 7, health care workers at this hospital report a respiratory illness.
March 5, 2003	A Hotel M contact dies in Toronto; 5 family members are affected.
March 12, 2003	WHO issues a global alert.
March 14, 2003	Singapore and Toronto report clusters of atypical pneumonia. In retrospect, both groups have an epidemiologic link to Hotel M. During travel, symptoms develop in one of the doctors who treated patients in Singapore; he is quarantined in transit on arrival in Germany.
March 15, 2003	WHO has received reports of more than 150 cases of the new disease, now named the severe acute respiratory syndrome (SARS). A travel advisory is issued.
March 17, 2003	WHO multicenter laboratory network established for the study of SARS causation and diagnosis.
March 21–27, 2003	A novel coronavirus is identified in patients with SARS.
April 12, 2003	Mapping of the full genome of SARS-associated coronavirus (soon called SARS-CoV) is completed.
April 16, 2003	WHO announces that SARS-CoV is the causative agent of SARS.
June 2003	A virus related to SARS-CoV is isolated from animals.
July 5, 2003	The absence of further transmission in Taiwan signals the end of the SARS outbreak in humans.
September 2003	Laboratory-acquired SARS-CoV infection reported in Singapore.

\* WHO denotes World Health Organization.

China.<sup>19</sup> SARS-like coronaviruses were isolated from Himalayan palm civets (*Paguma larvata*) and from a raccoon dog (*Nyctereutes procyonoides*) in one market in Guangdong Province where wild game animals are sold. In addition, persons in-

involved in the wild-animal trade in Guangdong Province had a higher seroprevalence of SARS-CoV than workers in other parts of the market or unrelated controls.<sup>20</sup> These findings support the hypothesis that SARS-CoV originated from animals and point to markets that trade in live game animals as potential sites of interspecies transmission. Experiments have shown that the virus can also infect other small mammals such as ferrets and cats, causing disease in the former<sup>21</sup> — findings that may have epidemiologic relevance. Studies in trapped wild animals and domestic animals and the genetic analysis of viruses isolated from them will help to define the animal reservoir of the virus in nature.

#### EPIDEMIOLOGY

To date, there have been a few preliminary attempts at modeling that will permit the quantitative assessment of the epidemic potential of SARS and the effectiveness of control measures. The results indicate that the SARS-CoV is less transmissible than was initially thought, with the average number of secondary cases resulting from each case estimated to be two to four overall. However, one feature of this disease is that a few infected persons have been responsible for a disproportionate number of transmissions — the so-called super-spreading events.<sup>18,22-27</sup> These results suggest that SARS-CoV is sufficiently transmissible to cause a very large epidemic if it is left unchecked but that it is not so contagious overall as to be uncontrollable with good, basic public health measures.<sup>23,24,26</sup>

Most studies of SARS cases in which transmission occurred from a single point of exposure estimated the incubation period to be between 2 and 10 days, with a median ranging from 4 to 7 days.<sup>26-28</sup> However, with the application of maximum-likelihood methods, the mean incubation period was calculated to be 6 days, and the maximal incubation period 14 days.<sup>22</sup> Recent studies in China indicate that some cases may have developed after incubation periods of up to 20 days, although data on the history of exposure were incomplete.<sup>29</sup> However, public health measures based on the maximal incubation period of 10 days, which the World Health Organization (WHO) estimated on the basis of studies, were successful in interrupting the chain of infection globally. It is not clear whether the route of infection influences the incubation period.<sup>26</sup>

Although some asymptomatic and mild infections have been documented, they seem to be

uncommon<sup>26,30,31</sup> and do not appear to contribute to the extension of the chain of infection among humans. For example, a recent mild infection with SARS-CoV acquired in the laboratory was not transmitted to any contacts of the affected person.<sup>32</sup> Despite numerous attempts, there has been no documented isolation of the virus from persons with asymptomatic infections, and in recent serologic and epidemiologic studies, transmission from persons with asymptomatic cases to contacts could not be detected.<sup>18,31</sup> SARS-CoV RNA was detected in four asymptomatic, quarantined persons in Hong Kong, with seroconversion in one, but no virus could be isolated.<sup>18</sup>

SARS has been transmitted primarily, but not exclusively, in health care and hospital settings, generally five or more days after the onset of disease and from patients who were severely ill.<sup>22,24,26</sup> These observations correlate with the finding that the peak viral load is reached around the 10th day of illness.<sup>11,12</sup> There has been no reported instance of transmission before the onset of symptoms of disease. Transmission to casual and social contacts is uncommon, but transmission has occurred occasionally after close contact with a patient with SARS in the workplace, on an airplane, or in a taxi.<sup>26</sup> Although virus can be detected by RT-PCR for more than 30 days after the onset of illness, it is difficult to isolate the virus after the third week of disease.<sup>12</sup> This difficulty is consistent with the epidemiologic observation that no transmission has been documented more than 10 days after the resolution of fever.<sup>26</sup>

The primary mode of transmission appears to be through direct or indirect contact of mucous membrane (eyes, nose, or mouth) with infectious respiratory droplets or fomites.<sup>3,26,27</sup> The use of aerosol-generating procedures (such as endotracheal intubation, bronchoscopy, and treatment with aerosolized medication) in hospitals may amplify the transmission of SARS-CoV, and outbreaks have involved more than 100 patients on occasion.<sup>3,26-28</sup> SARS-CoV survives for many days when dried on surfaces and in feces at an alkaline pH.<sup>33</sup> Although data from direct comparisons are not yet available, a review of previously published data suggests that SARS-CoV may be far more stable than other human respiratory viruses, such as respiratory syncytial virus. The role of fecal-oral transmission is unknown but may be important, given that profuse watery diarrhea is a common feature of the disease and that SARS-CoV is shed in large quantities in

stool.<sup>11</sup> There have been no reports of foodborne or waterborne transmission; however, studies are needed to determine whether these routes have any role.<sup>26</sup>

In some instances, other modes of transmission have clearly been relevant. For example, given the point-source nature and the temporal and spatial progression of the community outbreak that affected more than 300 persons in the Amoy Gardens apartment complex in Hong Kong, it is unlikely to have been caused solely by transmission through respiratory droplets or contact. The leading hypothesis is that small virus-containing droplets from contaminated sewage entered the bathrooms of the apartment complex through dried-up U-traps,<sup>34</sup> but other contributory factors cannot be ruled out.<sup>35,36</sup>

To date, there have been two reported cases of transmission from children to adults and no reports of transmission from children to other children.<sup>26,37</sup> There have been no reports of vertical or perinatal transmission.<sup>38</sup>

A combination of tracing of contacts and molecular epidemiologic data provides a better understanding of the genesis of the SARS pandemic. For instance, contact tracing suggested that a 65-year-old physician from Guangdong Province who stayed for one day at a hotel ("Hotel M") in Hong Kong on March 21, 2003, transmitted the virus to a number of guests who, on their return or further travel to Vietnam, Singapore, and Toronto, initiated local transmission and contributed to the global dissemination of the disease.<sup>27,39,40</sup>

Molecular epidemiologic studies indicate that viruses from the outbreaks in Hong Kong, Vietnam, Singapore, Toronto, and Taiwan are clonally related, whereas those from Guangdong Province are genetically more diverse.<sup>41-43</sup> Although there is evidence that other SARS-CoVs were introduced into Hong Kong in February 2003, all of them belonging to genetic lineages distinct from that of the index case in Hong Kong, none of these viruses appear to have generated a substantial number of secondary cases or contributed to the subsequent outbreak in Hong Kong.<sup>43</sup> This observation raises the question of whether some viral lineages are more prone to transmission than others. Further molecular epidemiologic data from mainland China may help to address this question. However, viral factors by themselves are an inadequate explanation for super-spreading events, since most patients infected in a super-spreading incident are not super-spreaders themselves. Other biologic and behavioral fac-

tors in the host, as well as environmental factors, may contribute to such incidents. Undetected cases in hospitals and the use of aerosol-generating procedures may explain some, but not all, super-spreading events.<sup>26,44</sup>

The role of seasonality in the transmission of SARS-CoV is currently unknown. Many respiratory viruses, including the human coronaviruses (e.g., 229E), are most common in the winter. However, this is not true of all respiratory viruses and all geographic regions. For example, the transmission of respiratory syncytial virus (and sometimes influenza) in Hong Kong is maximal during the summer, and the SARS outbreak in China peaked at the end of April, about two to three months after the usual peak of influenza activity in the northern Chinese provinces.

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#### THE CLINICAL DISEASE

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SARS has affected persons in all age groups; there has been a slight predominance of female patients, which is probably related to the increased likelihood of exposure among nurses.<sup>22</sup> SARS has also been reported in immunocompromised patients and pregnant women, but the numbers of reported cases are too small to permit any judgment as to whether the outcome was more or less severe in such patients.<sup>38,45,46</sup>

Infected persons present initially with fever, myalgia, malaise, and chills or rigor (Table 2).<sup>1,3,5,11,14,40,47-51</sup> Cough is common, but shortness of breath, tachypnea, or pleurisy is prominent only later in the course of the illness. Unlike other atypical pneumonias caused by mycoplasma or chlamydia, SARS is less commonly manifested as upper respiratory symptoms such as rhinorrhea and sore throat. A watery diarrhea occurs in some patients later in the course of the illness (Table 2). Respiratory signs such as rales are present in less than one third of cases, and their severity often seems lower than would be expected on the basis of the findings on radiography of the chest.<sup>5</sup> Afebrile cases of SARS can occur in the elderly, who may present with malaise and decreased appetite. In such patients, the presenting problem may even be a fall and fracture.<sup>52</sup>

Lymphocytopenia is common, and in some patients the platelet count is depressed, with concomitant increases in the level of D-dimers and the activated partial-thromboplastin time (Table 3).<sup>1,3,5,11,14,40,47,49</sup> The levels of alanine amino-

transferase, creatine kinase, and lactate dehydrogenase may be increased. However, these laboratory findings do not allow reliable discrimination between SARS and other causes of community-acquired pneumonia.<sup>53</sup> Depending on the interval between the onset of fever and hospital admission, the initial chest radiograph is abnormal in 60 to 100 percent of cases (Table 4).<sup>54-63</sup> A high-resolution computed tomographic (CT) scan is abnormal in 67 percent of patients with initially normal chest radiographs.<sup>62</sup> The most common initial radiographic abnormalities are ground-glass opacifications that do not obscure the view of underlying vessels or focal consolidations of the peripheral, subpleural, and lower zones of the lungs (Table 4). Mediastinal lymphadenopathy, cavitation, and pleural effusions are rare.

One third of patients with SARS have improvement, with defervescence and resolution of radiographic changes.<sup>46</sup> The other two thirds have persistent fever, increasing shortness of breath, tachypnea, oxygen desaturation, worsening of chest signs on physical examination, and the onset of diarrhea.<sup>11</sup> Serial chest radiographs or CT scans reveal the progression of the original abnormality into unilateral or bilateral multifocal air-space consolidations.<sup>46,59,60</sup> Shifting or fluctuating radiographic shadows have been noted. Pneumomediastinum without preceding positive-pressure ventilation or intubation is a characteristic radiographic sign of SARS.<sup>11</sup> The subpleural pneumonic process may cause a pleurodesis-like effect, and the diffuse alveolar damage has led to fibrosis and the formation of cysts. The air leak resulting from the rupture of these cysts can only dissect along the bronchovascular bundle, thereby causing pneumomediastinum, an unusual complication.

About 20 to 30 percent of patients require admission to an intensive care unit, and most of them require mechanical ventilation.<sup>3,5,11,14,40,47-49</sup> A low-tidal-volume strategy for the protection of the lungs has usually been used for ventilation, with volume-control or pressure-control ventilation targeting tidal volumes of 6 ml per kilogram of predicted body weight and plateau pressures of less than 30 cm of water.<sup>64</sup> Positive end-expiratory pressure, the fraction of inspired oxygen, and the ventilator rates have then been adjusted to maintain a partial pressure of arterial oxygen of more than 55 mm Hg (oxygen saturation as measured by pulse oximetry, >88 to 90 percent), with or without permissive hypercapnia. The terminal event has been

**Table 2. Initial Clinical Presentation of Adults with SARS.\***

Variable	China	Hong Kong	Canada	Singapore	All Four Countries
<b>Demographics</b>					
No. of cases reported	190	388	154	20	752
Age of patients — yr	Range, 16–84	Mean, 42.9	Median, 45	Median, 28	NA
<b>Sex</b>					
Male — no.	70	174	94	5	343
Female — no.	120	214	60	15	409
Ratio of male to female	0.58:1	0.8:1	1.57:1	0.33:1	0.84:1
<b>Clinical features — no./total no. (%)</b>					
Fever	190/190 (100.0)	388/388 (100.0)	153/154 (99.4)	20/20 (100.0)	751/752 (99.9)
Chill or rigors	89/190 (46.8)	245/378 (64.8)	40/144 (27.8)	3/20 (15.0)	377/732 (51.5)
Myalgia	114/190 (60.0)	169/388 (43.6)	73/154 (47.4)	9/20 (45.0)	365/752 (48.5)
Malaise	179/190 (94.2)	72/175 (41.1)	57/154 (37.0)	9/20 (45.0)	317/539 (58.8)
Rhinorrhoea	NM	44/198 (22.2)	3/144 (2.1)	3/20 (15.0)	50/362 (13.8)
Sore throat	NM	65/378 (17.2)	21/154 (13.6)	5/20 (25.0)	91/552 (16.5)
Cough	175/190 (92.1)	162/338 (47.9)	108/154 (70.1)	15/20 (75.0)	460/702 (65.5)
Dyspnea	175/190 (92.1)	31/250 (12.4)	68/154 (44.2)	8/20 (40.0)	282/614 (45.9)
Chest pain or pleurisy	41/190 (21.6)	3/10 (30.0)	3/10 (30.0)	NM	47/210 (22.4)
Anorexia	NM	37/188 (19.7)	NM	NM	37/188 (19.7)
Nausea or vomiting	NM	NM	1/10 (10.0)	7/20 (35.0)	8/30 (26.7)
Diarrhea	46/190 (24.2)	45/303 (14.9)	39/154 (25.3)	NM	130/647 (20.1)
Headache	116/190 (61.1)	118/388 (30.4)	54/154 (35.1)	4/20 (20.0)	292/752 (38.8)
Dizziness	89/190 (46.8)	68/263 (25.9)	6/144 (4.2)	NM	163/597 (27.3)
<b>Physical signs — no./total no. (%)</b>					
Tachycardia	NM	NM	71/154 (46.1)	NM	71/154 (46.1)
Tachypnea	NM	NM	60/154 (39.0)	NM	60/154 (39.0)
Chest rales	NM	19/50 (38.0)	37/154 (24.0)	NM	56/204 (27.5)

\* SARS denotes severe acute respiratory syndrome, NA not applicable, and NM not mentioned (in the relevant reports).

severe respiratory failure, multiple organ failure, sepsis, or intercurrent medical illness such as acute myocardial infarction.

Residual ground-glass opacifications have been noted on follow-up chest radiographs and CT scans obtained about one month after admission in 80 percent and 95 percent of patients, respectively, who recovered from SARS. CT scans have shown signs of fibrosis (including traction bronchiectasis and parenchymal bands) and peribronchovascular interstitial thickening.<sup>58</sup> Between 6 and 20 percent of discharged patients have had some degree of respiratory impairment that might be related to residual lung fibrosis, muscle weakness, and systemic effects of the viral illness.<sup>65</sup> Post-traumatic stress disorder and depression are common among patients with SARS and persist beyond the period of hospitalization.<sup>66</sup> Further follow-up is

required for the detection of other long-term complications of corticosteroid treatment, such as avascular necrosis of bone.

Pathological analysis of the lung at autopsy in patients who died within 10 days after the onset of illness revealed diffuse alveolar damage, desquamation of pneumocytes, an inflammatory infiltrate, edema, and hyaline-membrane formation. In patients who died later in the course of illness, organizing diffuse alveolar damage was seen, with squamous metaplasia and multinucleate giant cells of either macrophage or epithelial-cell origin.<sup>3,6,67,68</sup> Viral RNA was detectable by RT-PCR at high viral loads in the lung, bowel, and lymph nodes but was also detectable in the spleen, liver, and kidney.<sup>69</sup> In lung specimens, alveolar epithelial cells and, to a lesser extent, macrophages and bronchial epithelial cells showed evidence of viral antigen on im-

**Table 3. Initial Laboratory Abnormalities in Patients with SARS.\***

Variable	China	Hong Kong	Canada	Singapore	All Four Countries
Anemia	NM	17/135 (12.6)	NM	NM	17/135 (12.6)
Leukopenia	46/190 (24.2)	66/273 (24.2)	2/9 (22.2)	NM	114/472 (24.2)
Lymphocytopenia	NM	192/273 (70.3)	86/153 (56.2)	18/20 (90.0)	296/446 (66.4)
Thrombocytopenia	25/190 (13.2)	112/273 (41.0)	3/9 (33.3)	NM	140/472 (29.7)
Elevated serum alanine aminotransferase level	126/190 (66.3)	77/273 (28.2)	5/9 (55.6)	NM	208/472 (44.1)
Elevated serum lactate dehydrogenase level	50/190 (26.3)	98/138 (71.0)	4/5 (80.0)	NM	152/333 (45.6)

\* Lymphocytopenia was defined as an absolute lymphocyte count of less than 1500 per cubic millimeter in Singapore and as an absolute lymphocyte count of less than 1000 per cubic millimeter in Hong Kong and Canada; thrombocytopenia was defined as a platelet count of less than 100,000 per cubic millimeter in China and as a platelet count of less than 150,000 per cubic millimeter in Hong Kong and Canada; elevated serum levels of alanine aminotransferase and lactate dehydrogenase were defined as levels exceeding the upper limit of normal in China and Hong Kong and as levels that were more than 1.5 times the upper limit of normal in Canada. SARS denotes severe acute respiratory syndrome, and NM not mentioned (in the relevant reports).

munohistochemical analysis (Nicholls J: personal communication) and on in situ hybridization.<sup>70</sup>

#### DIAGNOSIS

SARS is a viral pneumonia that progresses rapidly. The initial manifestations of SARS are not specific,

and it cannot be clinically differentiated from other acute community-acquired pneumonias. The occurrence of lower respiratory disease, particularly pneumonia, in epidemiologically linked clusters of patients raises the level of suspicion but is not unique to SARS. Diseases such as influenza can cause similar outbreaks. The case definition of SARS has been refined over time.<sup>71,72</sup> During a hospital outbreak in Hong Kong, an emergency-room study showed that the initial case definition of suspected SARS that was published by the WHO had a sensitivity of 26 percent and a specificity of 96 percent.<sup>51</sup> Additional cases were uncovered through daily clinical and radiographic follow-up evaluation of epidemiologically linked patients who did not meet a sufficient number of criteria to satisfy the case definition. Given the lack of characteristic clinical features associated with SARS, the definition of cases had to rely heavily on the contact history of known patients.

The RT-PCR tests that were in use during April and May 2003 lacked sensitivity during the first five days of illness but had better sensitivity in later stages of the illness.<sup>12</sup> However, it was demonstrated that respiratory and fecal specimens are suitable for diagnosis with the use of RT-PCR. Although specimens from the lower respiratory tract are the most useful for viral diagnosis, few patients with SARS have a productive cough early in the course of illness. Thus, nasopharyngeal aspirates and swabs and throat and nose swabs are the primary types of

**Table 4. Initial Radiographic Manifestations in Patients with SARS.\***

Variable	China	Hong Kong	Canada
No. of patients studied	28–52	73–138	1–40
Initially abnormal chest radiograph (%)	60.7–100	78.3	60–100
Initially abnormal CT scan (%)	100	53.4 <sup>†</sup>	80–100
Bilateral involvement (%)	17.9–63.4	45.3	41.7–100
Unilateral involvement (%)	34.6–82.1	54.6	50.0–58.3
Lower-zone involvement (%)	67.7	61.1–74.8	70–100
Ground-glass opacifications (%)	31.0–85.7	NM <sup>‡</sup>	66.7–100
Consolidation (%)	14.3–65.4	NM	50–100
Both ground-glass opacifications and consolidation (%)	NM	NM	0–16.7
Pleural effusions (%)	NM	NM	5

\* SARS denotes severe acute respiratory syndrome, CT computed tomographic, and NM not mentioned (in the relevant reports).

<sup>†</sup> The rate is that for those with initially normal chest radiographs.<sup>56</sup>

<sup>‡</sup> Another radiographic study of follow-up CT scans (obtained an average of 36.5 days after admission) in Hong Kong demonstrated that 23 of 24 patients (96 percent) had residual ground-glass findings. Fifteen (62 percent) had signs of fibrosis and peribronchovascular interstitial thickening.<sup>57</sup>

specimens that have been investigated. Viral RNA is also detectable in serum or plasma, as well as in urine. More recently, improved methods of extracting specimens and real-time RT-PCR assays have improved the sensitivity of testing during the first few days of illness<sup>73</sup> and are now the mainstay for early diagnosis. When diagnostic tests are evaluated, it is important that the timing of specimen collection in relation to the onset of disease is defined. Furthermore, specimens collected during the first five days of illness should be tested because these are the specimens that are particularly difficult to assess for the presence of virus.

In the current context, with a low probability of a diagnosis of SARS, any positive laboratory result must be interpreted with caution in view of the possibility of laboratory error and serious implications of a positive result for global public health. An initially positive result on RT-PCR must be confirmed by testing another clinical sample, reextracting and testing the original specimen, and using assays that target different parts of the viral genome (e.g., polymerase and nucleocapsid). RT-PCR cannot be used to rule out infection.

The identification of seroconversion on a whole-virus immunoassay (an immunofluorescence assay or an enzyme-linked immunosorbent assay) remains the gold standard for the retrospective virologic confirmation of SARS-CoV infection, but antibody is detectable only after the first week of illness. The detection of IgM antibody does not appear to permit earlier diagnosis. Since a few patients with SARS have had late seroconversion, it is best to test a serum sample collected during the convalescent phase, at least 21 days and preferably 28 days after the onset of symptoms, in order to rule out SARS.<sup>11</sup>

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#### PROGNOSTIC FACTORS

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Age and coexisting illness, especially diabetes mellitus and heart disease, are consistently found to be independent prognostic factors for the risk of death and the need for intensive care (Table 5).<sup>3,11,46,48,49</sup> In patients older than 65 years of age, the mortality rate exceeds 50 percent. In some studies, an increased lactate dehydrogenase level and an elevated neutrophil count at the time of admission,<sup>3,46</sup> as well as low CD4 and CD8 lymphocyte counts,<sup>74</sup> were associated with a poor prognosis. SARS in children, especially those younger than 12 years of age, is generally associated with an uneventful course and a good outcome.<sup>37,75,76</sup>

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#### MANAGEMENT AND PREVENTION

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Although a number of strategies have been used for specific treatment and prevention, controlled studies documenting the efficacy of therapies are lacking. Patients with suspected SARS are initially treated empirically with broad-spectrum antibacterial drugs that are effective against other agents that cause typical and atypical acute community-acquired pneumonia to exclude these diagnoses.<sup>3,5</sup> Before the causative agent was known, ribavirin was used by some as a broad-spectrum empirical antiviral agent for the treatment of patients with SARS.<sup>3,11,14,40,77</sup>

Testing for susceptibility to antiviral drugs suggests that interferon beta, glycyrrhizin (licorice-root extract), and to a lesser extent, interferon alfa have activity against SARS-CoV.<sup>78,79</sup> In an experimental macaque model of SARS-CoV infection, treatment both before exposure and after exposure with pegylated interferon alfa reduced viral replication (unpublished data), and preliminary uncontrolled studies of combinations of interferon and corticosteroids in humans suggest that there are no obvious adverse effects.<sup>1,80</sup> Randomized, placebo-controlled clinical trials appear to be warranted.

There are a number of potential targets for antiviral drugs in the replication cycle of SARS-CoV, including fusion inhibitors and protease inhibitors.<sup>81</sup> The availability of the full genome sequence of the virus provides the basis for targeted strategies to develop antiviral drugs and vaccines.<sup>82</sup>

The pathogenesis of SARS is still incompletely understood. Unlike other acute respiratory viral infections, SARS is characterized by a peak in the viral load in respiratory secretions occurring around the 10th day of illness and a subsequent decrease, concomitant with the appearance of an antibody response to the virus.<sup>11</sup> Some patients have deterioration during the second week of illness in spite of a decreasing viral load, and it has been suggested that part of the damage to the lungs may be immunopathologic in nature.<sup>11,67</sup> Some have reported that early therapy with regimens of high-dose methylprednisolone is useful in modulating the damage to the lungs,<sup>1,77,83</sup> but no data from randomized, placebo-controlled trials are available to confirm a clinical benefit. A number of other therapeutic options, including thymic peptides or recombinant human thymus proteins, intravenous immunoglobulin, IgM-enriched immunoglobulin, plasma from patients in the convalescent phase, and traditional

**Table 5. Multivariate Analysis of Risk Factors for Adverse Outcomes in Patients with SARS.\***

Adverse Outcome	Risk Factors	Relative Risk or Odds Ratio (95% CI)†	P Value	Source
Death, ICU admission, or mechanical ventilation	Diabetes mellitus	3.1 (1.4–7.2)	<0.01	Booth et al. <sup>49</sup>
	Other coexisting conditions	2.5 (1.1–5.8)	0.03	
Death or ICU admission	Advanced age (per 10-yr increment)	1.8 (1.16–2.81)	0.009	Lee et al. <sup>3</sup>
	High peak lactate dehydrogenase level (per increment of 100 U/liter)	2.09 (1.28–3.42)	0.003	
	Neutrophil count above normal limit on admission	1.6 (1.03–2.50)	0.04	
Development of acute respiratory distress syndrome at day 21	Age of 61–80 yr	28.0 (3.1–253.3)	0.003	Peiris et al. <sup>11</sup>
	Positive test for hepatitis B surface antigen	18.0 (3.2–101.3)	0.001	
Death	Age >60 yr	3.5 (1.2–10.2)	0.02	Chan et al. <sup>48</sup>
	Diabetes mellitus or heart disease	9.1 (2.8–29.1)	<0.001	
	Another coexisting condition	5.2 (1.4–19.7)	0.01	
Death or ICU care	Advanced age (per 10-yr increment)	1.57 (1.26–1.95)	<0.001	Tsui et al. <sup>46</sup>
	Neutrophil count on admission (per increment of 100 cells/mm <sup>3</sup> )	1.28 (1.13–1.46)	<0.001	
	Initial lactate dehydrogenase level (per increment of 100 U/liter)	1.35 (1.11–1.64)	0.003	

\* SARS denotes severe acute respiratory syndrome, CI confidence interval, and ICU intensive care unit.

† Data from the study by Booth et al.<sup>49</sup> are relative risks; all other data are odds ratios.

Chinese medicine, have been used, but their clinical efficacy is unclear.<sup>1,83-85</sup>

In the absence of a vaccine, preventing the transmission of SARS involves triage, early case detection and isolation of patients to prevent transmission within hospitals, public education, contact tracing and quarantine of contacts to prevent community transmission, and surveillance at border crossings through health-declaration forms and the monitoring of persons for fever. Nosocomial spread has been one of the major epidemiologic features of SARS outbreaks,<sup>3,27,28,40,86</sup> and the elimination of hospital transmission through enhanced infection-control practices is an important control measure. We have not attempted to provide a comprehensive review of infection-control measures for SARS. Precautions against transmission through respiratory droplets and contact precautions are critical in preventing the bulk of hospital transmission.<sup>71,72,87</sup> In addition, precautions against airborne transmission have been recommended and

are clearly needed when aerosol-generating procedures are being undertaken.<sup>71,88,89</sup>

Patients with unrecognized SARS, especially those with an atypical presentation, the elderly, and the chronically ill, have been the source of a number of outbreaks and pose a challenge to infection control in hospitals.<sup>89</sup> Thus, a high index of suspicion is required in the recognition of cryptic cases of SARS, and infection-control standards must be reinforced in all parts of the hospital. Given the stability of SARS-CoV in the environment,<sup>33</sup> strict hand hygiene and training in the use of postexposure prophylaxis (especially degowning) is particularly critical in preventing the transfer of virus through fomites and from protective equipment to the body. Communication about risk through public education is vital in order to maintain the correct balance between public awareness and anxiety, so that meaningful public health measures can be implemented without causing economic and social paralysis.

## CONCLUSIONS

Like many of the other 30 or so new pathogens that have been recognized in the past three decades, SARS-CoV may have originated in animals. However, unlike most of these other pathogens, it has become efficient at human-to-human transmission, and this development accounts for the global scale of the disease. In this respect, SARS-CoV resembles the human immunodeficiency virus. The SARS outbreak also serves to illustrate the potential health effects of more transmissible diseases, such as pandemic influenza, and highlights the need for preparedness to meet such threats.

It is difficult to make predictions regarding the resurgence of SARS, but the current information suggests that the greatest risk of the reemergence of the disease may derive from an animal reservoir or infections transmitted in the laboratory.<sup>20,32</sup> Appropriate containment measures in diagnostic and research laboratories must therefore be strength-

ened. Given the fact that SARS-CoV has been isolated from some animals used for food, decisions about reintroducing such animal species into exotic-food markets must be based on a proper assessment of the risks involved. SARS-CoV may also survive between seasons, owing to unrecognized ongoing disease transmission in humans in some parts of the world — for example, asymptomatic carriers or immunocompromised patients. However, current data suggest that these are less likely to be a source of the reemergence of SARS.

Active surveillance for clusters of cases of severe respiratory disease must be a priority, especially among health care workers. Such surveillance should include the rapid diagnosis and prevention of other respiratory viruses that cause outbreaks of febrile respiratory disease — notably, influenza. Surveillance and astuteness on the part of clinicians are the keys to the early detection of any reemergence before it regains a foothold in the community.

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