

# Severe Acute Respiratory Syndrome

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**The first cases of severe acute respiratory syndrome (SARS) occurred in China in November 2002. The agent causing this illness has been identified as a novel coronavirus, SARS-coronavirus. Since its introduction <1 year ago, this virus has infected 8098 people in 26 countries, killing 774 of them. We present an overview of the epidemiology, clinical presentation, diagnosis, and treatment of SARS based on the current state of knowledge derived from published studies and our own personal experience.**

On 11 February 2003, the Program for Monitoring Emerging Diseases (<http://www.promedmail.org>) reported that, since November 2002, an unidentified agent had caused some 300 cases of pneumonia in persons in the south of China. On 12 March 2003, the World Health Organization (WHO) issued a global alert regarding these and similar cases in Hong Kong and Vietnam. This clinical syndrome subsequently became known as "severe acute respiratory syndrome" (SARS). Since then, 8098 people in 26 countries have had probable SARS diagnosed, 774 of whom have died (figure 1), yielding a global case-fatality rate of ~10% [1, 2]. On 5 July 2003, the WHO reported that the last known human chain of transmission of SARS had been broken [3].

A newly discovered coronavirus (SARS-CoV) has been identified as the cause of SARS [4–7]. SARS-CoV-like viruses have been detected in Himalayan palm civets and a raccoon-dog in a market in southern China, suggesting that the origin of SARS-CoV may have been from these or other wild animals [8]. Given the possibility that human or animal reservoirs of SARS-CoV may still exist and that SARS may have a seasonal predilection, there is concern that SARS may return in upcoming respiratory seasons. WHO guidelines emphasize the need for all countries to remain vigilant and to maintain their capacity to detect and respond to the potential reemergence of SARS [9].

## EPIDEMIOLOGY

SARS remained isolated in China from November 2002 until 21 February 2003, when a physician with SARS traveled from Guangdong province to a hotel in Hong Kong, infecting 10 other guests [9]. The movements of these 11 individuals resulted in the spread of SARS worldwide and sparked all of the major epicenters outside of China [1] (figure 2).

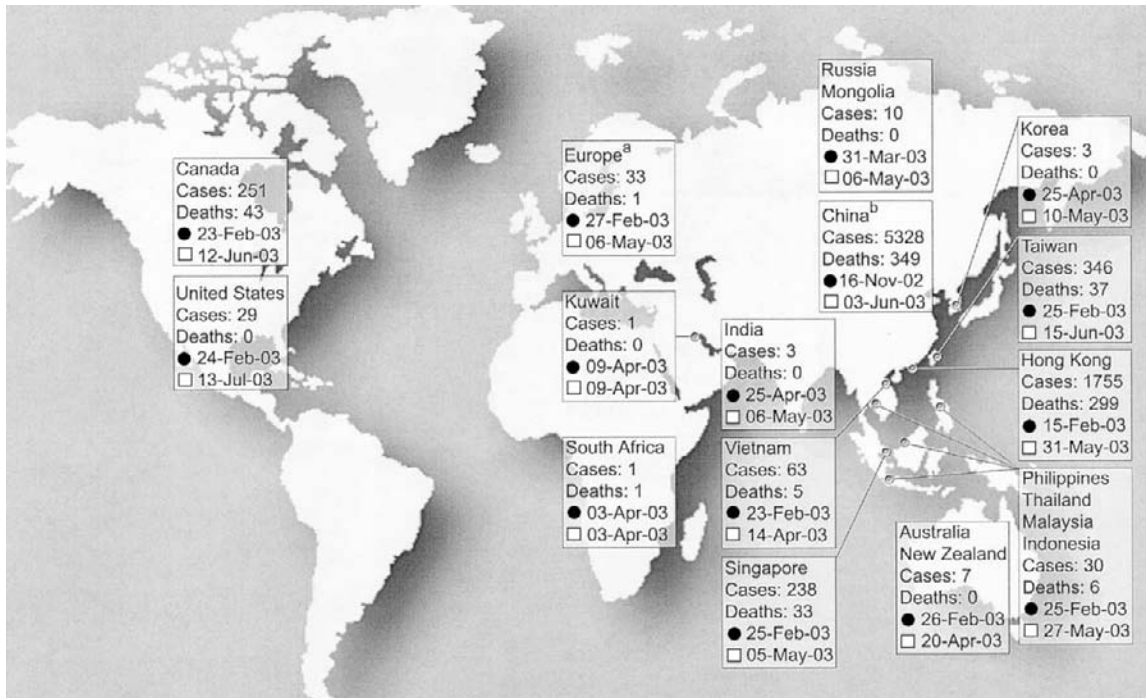
The rate of spread of an epidemic and whether it is self-sustaining depend on the basic reproduction number ( $R_0$ ).  $R_0$  is defined as the average number of secondary cases generated by 1 primary case in a susceptible population [10]. This quantity determines the potential for an infectious agent to start an outbreak, the extent of transmission in the absence of control measures, and the ability of control measures to reduce spread. During the course of an epidemic,  $R_t$ , the effective reproduction number, decreases in comparison with  $R_0$  as a result of the depletion of susceptible persons in the population, death or recovery with subsequent immunity, and the implementation of specific control measures. To stop an outbreak,  $R_t$  must be maintained below 1. Mathematical modeling of the early phase of the Singapore and Hong Kong outbreaks, before the institution of control measures and during which time it was occurring primarily in the hospital setting, estimated that the  $R_0$  was 2.2–3.7, indicating that the virus is moderately infective [11, 12]. The attack rate for SARS-CoV ranges from 10.3% to 60% or 2.4 to 31.3 cases/1000 exposure-hours, depending on the clinical setting and the unit of measurement [13]. A significant limitation of these calculations is that these data are based on diagnoses made with a clinical case definition. Reanalysis will be required once the results of seroprevalence studies are completed and will provide a more accurate estimate of  $R_0$ .

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**Figure 1.** Probable cases of severe acute respiratory syndrome reported worldwide between 1 November 2002 to 31 July 2003 [1]. <sup>a</sup>Includes France, Germany, Ireland, Italy, Romania, Spain, Sweden, Switzerland, and United Kingdom. <sup>b</sup>Includes Macao. ●, Date of onset of first probable case; □, Date of onset of last probable case.

## MECHANISMS AND ROUTES OF TRANSMISSION

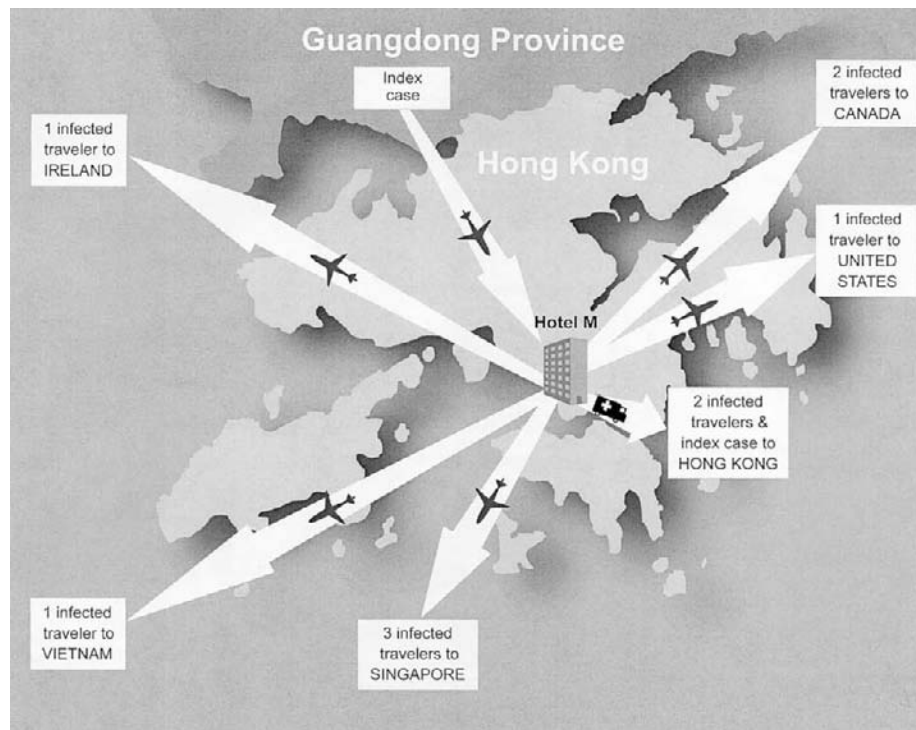
SARS-CoV has been isolated in sputum samples, nasal secretions, serum specimens, feces samples, and bronchial washings [5, 14]. Evidence suggests that SARS-CoV is transmitted by contact and/or droplets [6, 15] and that the use of any mask (surgical or N95) significantly decreases the risk of infection [16]. However, there are cases that defy explanation based on these modes of transmission, suggesting that alternative modes of transmission may also exist [13, 17]. SARS-CoV remains viable in feces for days [18], and the outbreak at the Amoy Gardens apartments highlights the possibility of a fecal-oral or fecal-droplet mode of transmission [19, 20]. A number of cases occurred in health care workers wearing protective equipment following exposure to high-risk aerosol- and droplet-generating procedures, such as airway manipulation, administration of aerosolized medications, noninvasive positive pressure ventilation, and bronchoscopy or intubation [17, 21, 22]. When intubation is necessary, measures should be taken to reduce unnecessary exposure to health care workers, including reducing the number of health care workers present and adequately sedating or paralyzing the patient to reduce cough. Updated infection control precautions for patients who have SARS are available from the Centers for Disease Control and Prevention (CDC) at <http://www.cdc.gov/ncidod/sars/index.htm>.

Currently, epidemiological evidence suggests that transmission does not occur before the onset of symptoms or after symptom resolution, even though shedding of SARS-CoV in stool has been documented by RT-PCR for up to 64 days after the resolution of symptoms [23]. A small group of patients appear to be highly infectious and have been referred to as “super-spreaders” [24]. Such events appear to have played an important role early in the epidemic. Possible explanations for their enhanced infectivity include the lack of early implementation of infection-control precautions, higher SARS-CoV load, and larger amounts of respiratory secretions.

## CLINICAL DISEASE

**Case definition.** Case definitions of SARS based on clinical and epidemiologic data were developed during the outbreak. Although these definitions were epidemiologically useful, Rainer et al. [25] have shown that they had a low sensitivity for diagnosis in patients early in disease (sensitivity, 26%; specificity, 96%), underscoring the importance of a rapid, accurate diagnostic test. Since then, the CDC has developed updated SARS surveillance case definitions based on clinical, epidemiologic, and laboratory criteria [26]. The WHO has similar updated definitions [27].

**Presentation.** The typical incubation period of SARS



**Figure 2.** Transmission of severe acute respiratory syndrome by a single individual from Guangdong province, China, to Hotel M in Kowloon, Hong Kong, and subsequently to countries around the world via air travel by infected hotel guests [9].

ranges from 2 to 10 days but may occasionally be as long as 16 days [21, 28]. The frequencies of symptoms at the onset of disease are summarized in table 1. The prodrome includes influenza-like symptoms, such as fever, myalgias, headache, and diarrhea [21, 28]. Fever can vary from low to high grade and can occasionally be absent at presentation, particularly in older patients. The typical respiratory phase starts 2–7 days after the prodrome and can be associated with watery diarrhea [14, 21, 28]. The early respiratory stage includes a dry, nonproductive cough and mild dyspnea. Early-phase chest radiographs often show subtle peripheral pulmonary infiltrates that can be more readily detected as consolidations having a ground-glass appearance with high-resolution CT of the lung [29, 30]. Atypical presentations of the disease have been described elsewhere [31, 32], including cases involving fever but no respiratory component [33]. Asymptomatic cases have also been described, but only in small numbers [34]. Of interest, the disease has been rare in children and, when present, has appeared to be milder [33, 35].

**Spectrum of disease.** After the onset of disease, cases may progress to a mild variant of the disease characterized by mild respiratory symptoms with fever or a “cough variant” characterized by persistent intractable cough. However, most commonly, cases progress to a moderate-severe variant characterized by a more serious later respiratory phase with dyspnea on exertion or at rest and hypoxia. This later respiratory phase

typically occurs 8–12 days after the onset of symptoms (table 2) [14, 21, 28]. In 10%–20% of hospitalized patients, persistent or progressive hypoxia results in the requirement of intubation and mechanical ventilation [28, 36, 37]. Among patients developing respiratory failure, intubation is required at a median of 8 days after onset of symptoms [35, 36]. Subtle but progressive decreases in oxygen saturation are often indicative of impending respiratory failure and should trigger more-intensive monitoring and preparation for intubation under controlled circumstances. Typically, the respiratory phase lasts ~1 week. The recovery phase begins ~14–18 days after the onset of symptoms.

**Clinical outcome.** The case-fatality rate during recent outbreaks was 9.6% (range, 0%–40%) [1]. Advanced age is the most important risk factor for death: patients aged >60 years have a case-fatality rate of 45% [14, 28]. Other risk factors for death include diabetes mellitus and hepatitis B virus infection [14, 21, 28, 36, 37]. Little data exist regarding the long-term morbidity of SARS, although preliminary studies suggest that the psychological impact of the disease is considerable [38, 39].

## LABORATORY DIAGNOSIS

Sensitive and specific tests for detection of SARS-CoV that can yield results within hours of patient presentation are urgently needed. Many tests have been developed, including some that

**Table 1. Summary of clinical findings of severe acute respiratory syndrome at admission to the hospital.**

Characteristic or symptom	Toronto [25] (n = 144)	Hong Kong [21] (n = 138)	Hong Kong [14] (n = 75)
Age, years			
Median (IQR)	45 (34–57)	...	...
Mean $\pm$ SD	...	39.3 $\pm$ 16.8	39.8 $\pm$ 12.2
Fever	99.3	100	100
Nonproductive cough	69.4	57.3	22
Myalgias	49.3	60.9	68
Dyspnea	41.7	NR	4
Headache	35.4	55.8	15
Malaise	31.2	NR	NR
Chills and rigors	27.8	73.2	65 and 56
Diarrhea	23.6	19.6	1
Nausea and vomiting	19.4	19.6	NR
Sore throat	12.5	NR	11
Arthralgia	10.4	NR	NR
Chest pain	10.4	NR	NR
Productive cough	4.9	29.0	NR
Dizziness	4.2	42.8	4
Abdominal pain	3.5	NR	NR
Rhinorrhea or coryza	2.1	22.5	NR

**NOTE.** Data are percentage of subjects, unless otherwise indicated. IQR, interquartile range; NR, not reported.

are now marketed commercially, but none have yet achieved this goal. The early diagnosis of SARS is based on recognition of epidemiological linkages; the presence of typical clinical, laboratory, and radiographic features; and the exclusion of other respiratory pathogens. None of these features of SARS are specific, however, and diagnosis should be confirmed by SARS-CoV-specific microbiological and serological studies, although initial management will continue to be based on a clinical and epidemiological assessment of the likelihood of SARS-CoV infection.

**Routine laboratory tests.** At the time of presentation, routine hematological and biochemical test findings are frequently abnormal. In particular, lymphopenia, thrombocytopenia, an absence of neutrophilia, elevated lactic dehydrogenase levels, and elevated creatine phosphokinase levels have been observed [14, 21, 28]. However, on the basis of preliminary analysis, when compared against the laboratory features of other causes of community-acquired pneumonia, none of these tests alone are sufficient to significantly alter the pretest probability of SARS [40].

**Testing for SARS-CoV.** Serologic assays for SARS-CoV include immunofluorescent assays, ELISAs, and Western blot assays. On the basis of the limited studies completed to date, IgM detection is delayed by ~1 week after the onset of symptoms, and the mean time to IgG seroconversion is estimated

to be between 20 and 26 days. As a result, serologic testing at presentation is not useful as a strategy for rapid diagnosis [14, 41, 42].

Assays for culturing SARS-CoV in cell lines and for its rapid detection by RT-PCR from clinical specimens are available. The sensitivity of culture is lower than that of RT-PCR [43]. The specificity of the RT-PCR assays can be assured by using specific probes, sequencing the RT-PCR product, or completing a second RT-PCR assay using primers amplifying a different genome region. Quality-control measures should be in place to prevent false-positive results due to laboratory contamination. The analytical sensitivity of these assays has been shown to be high, with reproducible detection limits of 10 copies of viral RNA [44]. However, on the basis of the results of first-generation assays, the clinical sensitivity of SARS-CoV RT-PCR has been estimated to be as low as 50%, depending on the type of specimens tested and the timing of collection relative to the onset of symptoms of SARS [6, 42]. Specimens that have the highest proportion positive for SARS-CoV using first-generation assays include nasopharyngeal swabs, nasopharyngeal aspirates, throat swabs, and stool (highest yield) [14, 42, 43]. Specimen obtainment ~10 days from symptom onset is associated with the highest yield for all specimen types, which correlates with the timing of peak virus loads [14]. Optimization of SARS-CoV RT-PCR assays with regard to the targeted genomic region, the

timing of specimen obtainment, the type of specimens, and the extraction methodology is ongoing. A recent report describes a second generation assay with a clinical sensitivity of 80% using a modified extraction method on nasopharyngeal aspirates obtained in the first 3 days of illness [45].

A summary of samples and tests to investigate possible SARS appears in table 3. Coinfections with SARS-CoV and other infectious agents can exist, and, as a result, finding an infectious agent other than SARS-CoV should not be used to rule out SARS [46].

## TREATMENT

At present, there is not sufficient evidence to recommend any specific therapy for the treatment of SARS. Because SARS cannot be easily distinguished from other causes of pneumonia, patients who are suspected of having SARS who have pulmonary infiltrates should receive appropriate antibiotic coverage [47]. Respiratory failure is the primary cause of acute morbidity and mortality due to SARS-CoV infection and occurs in 20%–25% of cases [21, 28, 37]. When mechanical ventilation is required, a “lung protective” ventilation strategy should be used based on an analogy to data for the treatment of acute respiratory distress syndrome (ARDS) and the current intensive care unit experience managing SARS [36, 37, 48]. In fact, barotrauma appears to be one of the most frequent complications of severe SARS-CoV infection, with pneumothorax and/or pneumomediastinum occurring in 20%–34% of ventilated patients, a rate that is much higher than the rate of 2.5% observed in a large study of ARDS [36, 37, 48].

**Antiviral therapy.** Antiviral agents used in the therapy of SARS include ribavirin, IFN- $\alpha$ , and lopinavir-ritonavir. Ribavirin is a nucleoside analogue with in vitro activity against a number of RNA and DNA viruses, including some animal coronaviruses [49]. Ribavirin was widely used for the treatment of SARS. Initial reports noted improvement in surrogate markers of outcome, such as resolution of fever and improvement in oxygenation and radiographic appearance [15, 21, 50]. These studies were not controlled, and most patients also received corticosteroids [15, 21, 50]. Other reports failed to identify improvement with ribavirin [28, 51], and one report identified a high frequency of adverse events among patients treated with

high-dose ribavirin, including severe hemolysis (in 49% of patients) [28]. In vitro testing of SARS-CoV indicated that ribavirin does not have activity against this virus at clinically achievable concentrations [52]. Postmortem findings for some patients demonstrated that high virus loads persisted despite treatment with ribavirin [53].

IFNs are cytokines with well-described antiviral activity [54]. IFNs, particularly IFN- $\beta$ , inhibit SARS-CoV in vitro [55]. An open-labelled study using IFN- $\alpha$  and high-dose methylprednisolone demonstrated more-rapid improvement in radiographic appearance and oxygenation in recipients, compared with a historic cohort that received a lower dose of corticosteroids alone [56]. A complex 4-arm trial examining ribavirin and IFN and differing doses of corticosteroids also demonstrated improvement in surrogate end points, such as radiographic appearance, but these improvements only occurred in the IFN recipients who also received high-dose corticosteroids [57].

Lopinavir-ritonavir is a combination drug consisting of 2 protease inhibitors with proven efficacy in the treatment of HIV. Lopinavir-ritonavir was studied in a nonrandomized open label study in Hong Kong as initial and rescue therapy for SARS. It was added to local standard therapy consisting of ribavirin and corticosteroids, and, when used as initial therapy, recipients had a significant reduction in the overall death rate and intubation rate, compared with a matched control group who received standard treatment alone. The control group, however, had lower rates of steroid use at lower mean doses, making definitive conclusions difficult [58].

**Anti-inflammatory therapy.** Anti-inflammatory or immunomodulatory therapies include corticosteroids, intravenous immunoglobulin (IVIG), and convalescent-phase serum and plasma exchange. Corticosteroids were widely used for SARS therapy. Preliminary results demonstrate decreasing virus loads and increasing antibody titers during the second week of illness, at a time when the respiratory disease typically progresses [14]. These results suggest that lung damage in patients with SARS-CoV infection may be immune mediated and provides the rationale for corticosteroid therapy. Pathological findings are consistent with cytokine dysregulation and provide further support for the theory that lung damage is immune mediated [52]. Initial case reports described resolution of fever and improvements in oxygenation and radiographic appearance in some patients treated with ribavirin and corticosteroids [59]. Subsequently, clinicians noted that cases in many patients progress despite receiving treatment with corticosteroids, and higher doses or pulsed steroid regimens were required as rescue therapy [60, 61]. A trial comparing early use of pulsed versus nonpulsed corticosteroids did not note any difference in the requirement for ventilation or mortality, but it did reveal improvements in oxygenation and radiographic appearance [62].

**Table 2. Duration of clinical phases of the mild and moderately severe variants of severe acute respiratory syndrome.**

Time	Phase			
	Prodrome	Respiratory		Recovery
		Early	Late	
From onset, days	0	2–7	8–12	14–18
Duration, days	2–7	1–10	5–10	5–7

**Table 3. Suggested tests for patients presenting with a high pretest probability of severe acute respiratory syndrome (SARS).**

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Suggested test
For identification of agents other than SARS-CoV
Blood culture
Routine culture of sputum and/or other lower respiratory specimens
Viral culture of sputum and/or other lower respiratory specimens in viral transport media
Obtainment of NP aspirate or NP swab in viral transport media for routine viral culture and direct fluorescent antibody/EIA routine virus testing (should minimally include testing for respiratory syncytial virus; influenza virus A and B; parainfluenza virus 1, 2, and 3; and adenovirus)
Obtainment of NP aspirate or NP swab in <i>Chlamydia</i> transport media for <i>Chlamydia pneumoniae</i> PCR (if available) or culture (if PCR is not available)
Obtainment of NP aspirate or NP swab in <i>Mycoplasma</i> transport media for <i>Mycoplasma pneumoniae</i> PCR (if available) or culture (if PCR is not available)
Also consider sending sputum/other respiratory specimens in a sterile container for <i>Legionella</i> culture and direct fluorescent antigen detection, as well as urine specimens for <i>Legionella</i> antigen detection, depending on clinical suspicion
Also consider sending sputum/other respirator specimens for <i>Mycobacterium</i> culture and susceptibility, depending on clinical suspicion
For identification of SARS-CoV <sup>a</sup>
Obtainment of serum samples for acute- and convalescent-phase serological examinations (the latter samples would be collected $\geq 28$ days after symptom onset)
Obtainment of lower respiratory specimens, NP aspirate, NP swab, and/or throat swab in viral transport media for SARS-CoV PCR and culture
Obtainment of stool specimen or rectal swab in viral transport media for SARS-CoV PCR and culture
Obtainment of whole blood samples in EDTA for SARS-CoV PCR and culture
Obtainment of autopsy tissue specimens in a sterile container flash frozen and stored at $-70^{\circ}\text{C}$ in a freezer

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**NOTE.** Completion of these tests for patients with a lower pretest probability in SARS should be considered for areas where sustained local SARS transmission occurred during the November 2002 to July 2003 outbreak, where there is a higher risk of SARS reemergence, compared with areas that had limited to no local transmission [1]. CoV, coronavirus; NP, nasopharyngeal.

<sup>a</sup> For all SARS-CoV PCR and culture testing, a baseline sample and serial samples thereafter (e.g., every 5 days) at least up to 10 days after onset of symptoms should be obtained to increase the sensitivity of SARS-CoV tests.

Concerns with the use of prolonged, high-dose, and pulsed corticosteroid regimens in the treatment of a new viral infection have been raised [62]. Pathological studies have detected high virus loads in patients who died >50 days into their illness and suggest that persistent viral replication is occurring and likely contributes to the pathophysiology of lung damage in SARS-CoV infection [53]. The use of corticosteroids could potentially increase or prolong viral replication and thereby worsen disease. Corticosteroids are also associated with a number of well-known adverse outcomes including immunosuppression and increased susceptibility to opportunistic pathogens, particularly those causing invasive fungal infections [63, 64]. In one multivariate analysis of 218 patients with SARS, use of pulsed corticosteroid therapy was strongly associated with mortality, although the results are difficult to interpret, because the sickest patients typically received pulsed corticosteroids as salvage therapy [65]. There have also been reports from China of avascular necrosis—a well-recognized complication of steroid therapy—occurring in patients who recovered from SARS [66]. IVIG consists of pooled antibodies from multiple donors. Although IVIG would not be expected to contain antibodies directed against SARS-CoV because of the low rate of background immunity in the population, it has been demonstrated to have other immunomodulatory properties and may down-regulate cytokine expression [67]. Convalescent-phase plasma samples have been used to treat SARS in Hong Kong and China and

may be of value because, unlike standard IVIG preparations, high levels of anti-SARS-CoV antibodies would be present [68]. Finally, plasma exchange was used as salvage therapy in Hong Kong, but no data exist with which to assess its efficacy [69].

## CONCLUSIONS

SARS is a deadly new infectious disease with the ability to spread from person to person and from country to country via international air travel. Despite the subsequent rapid spread of this virus worldwide, traditional public health measures were able to contain and control this outbreak. Because SARS-CoV causes a nonspecific clinical illness, diagnosing and controlling this disease in the future will require the development of rapid accurate tests. There is an urgent need to develop means of performing clinical trials that evaluate treatment regimens for SARS, as well as other new diseases, especially in outbreak situations.

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