

# Managing SARS amidst Uncertainty

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In November 2002, a businessman from the city of Foshan in the southern Chinese province of Guangdong may have been the first victim of a mysterious illness called severe acute respiratory syndrome (SARS). Guangdong Province, an agricultural area with a population of 75 million, has thousands of farms with large and small animals, a subtropical climate, and rainfall of about 2 m per year.

The first patient and many others received no international attention until February 2003, when a physician from Guangdong Province became ill while staying on the ninth floor of a hotel in Hong Kong. Twelve guests became infected, including at least seven who stayed in rooms on the ninth floor. These hotel guests subsequently became the index patients who transported the disease to Vietnam, Singapore, Canada, Ireland, and the United States. As of April 17, there had been 3389 cases and 165 deaths (a death rate of 4.9 percent) reported in 27 countries.

As reported in this issue of the *Journal*, microbiologic data from large groups at the Centers for Disease Control and Prevention (CDC) (pages 1953–1966) and in Europe (pages 1967–1976) strongly suggest that a novel coronavirus is the causative agent. Both teams isolated the virus in Vero-cell cultures, showed significant antibody responses in patients, and identified a unique coronavirus by gene sequencing. The European team found high concentrations of coronavirus RNA in sputum and low concentrations in plasma and feces from patients. The typical crown-like structure of coronavirus was identified at the CDC by electron microscopy of infected culture cells. Poutanen et al. (pages 1995–2005) isolated the new coronavirus in respiratory specimens from five of nine patients in Canada. Experimental studies have recently shown that the virus can infect primates, causing SARS.

Coronaviruses are ubiquitous and cause illness in many animals, including pigs, cattle, dogs, cats, and chickens. They have been associated with upper respiratory infections and sometimes pneumonia in humans. Genetic changes occur frequently, and the proximity of humans to animals in southern China

may have caused a recombinant animal virus to become an accidental tourist, crossing species to humans in Guangdong Province, leading to an epidemic among highly mobile and susceptible populations globally.

Although large-droplet transmission seems to be important in the spread of SARS, implying a requirement for intimate contact with a patient, the unusually rapid transmission suggests that airborne transmission through droplet nuclei (<10  $\mu\text{m}$  in diameter) can occur. Such droplet nuclei, which are key in the transmission of influenza, measles, and tuberculosis, allow the organisms to reach directly the alveoli of the lungs of contacts. Alternatively, viral contamination of the water supply or fomites might be important in some locales.

From the perspective of clinicians, all cases of community-acquired pneumonia are currently suspect, and a history of exposure to a patient with probable SARS increases the likelihood of the diagnosis. Suggestive laboratory features, as described by Lee et al. (pages 1986–1994), include lymphopenia, thrombocytopenia, and elevated lactate dehydrogenase levels. In patients with suspected SARS, a workup for known causes of community-acquired pneumonia should be performed, and specimens should be sent to the CDC for viral identification and serologic analysis (see Table).

In addition to the isolation of patients suspected of having SARS, with the use of negative-pressure rooms when feasible, we recommend that infection-control measures include the use of N95 masks, gloves, disposable gowns, and eye protection. Careful attention to hand washing or hand disinfection with an alcohol-based product after the removal of gloves is necessary. Grouping of exposed health care workers (cohorting) should be attempted, in order to minimize the number of persons who are exposed, and the number of visitors should be limited as much as possible. Disinfectants typically used in hospitals, including quaternary ammonium-based, phenol-based, and alcohol-based products, are highly active against coronaviruses.

Most physicians have prescribed standard

**Management of Suspected SARS.**

Isolate the patient
Place patient in private room (with negative pressure, if possible)
Wear gloves, gown, masks, eye protection
Wash hands carefully after removing gloves
Limit number of health care workers caring for patient
Limit number of visitors
Perform diagnostic studies
Obtain specimens to rule out causes of atypical pneumonia
Obtain specimens for SARS testing (see CDC Web page, <a href="http://www.cdc.gov/ncidod/sars/specimens.htm">http://www.cdc.gov/ncidod/sars/specimens.htm</a> )
Consider computed tomography of chest
Provide treatment
Supplementary oxygen for hypoxemia
Antibacterial agents for community-acquired pneumonia
Consider neuraminidase inhibitor for treatment of influenza
Ribavirin (oral formulation: 1.2 g every 8 hr; commercially available, intravenous form: 8 mg/kg of body weight every 8 hr) (available through the CDC)
Consider corticosteroids
Notify public health department

antibacterial regimens for community-acquired pneumonia, and some have added a neuraminidase inhibitor to cover both influenza virus A and influenza virus B. Until we have a predictive test for the causative agent of SARS, this approach is reasonable. Supplementary oxygen should be administered if the patient has hypoxemia. The antiviral drug ribavirin has been used extensively to treat SARS, but there are no data to show that it is effective. Intravenous administration was used in the patients who were most ill, and oral administration (resulting in bioavailability of approximately 50 percent) was used in other patients. In order to use the

intravenous form, a clinician in the United States must contact the CDC Emergency Operations Center (770-488-7100). Health Canada recently stated, however, that it will no longer provide access to ribavirin for the treatment of SARS, because of concern about its side effects and lack of *in vitro* efficacy.

Some physicians have also prescribed corticosteroids for patients with severe cases. A rationale for the use of corticosteroids derives from the pathological findings suggestive of cytokine dysregulation and hyperinduction of inflammatory mediators with diffuse alveolar damage. In the report by Lee et al., computed tomographic studies of the chest showed bilateral peripheral changes with ground-glass consolidation similar to that seen in bronchiolitis obliterans with organizing pneumonia. The latter is an inflammatory disease involving both terminal bronchioles and alveoli that usually responds to corticosteroids. In this time of uncertainty, we favor the use of corticosteroids only for the more ill patients. Because injectable methylprednisolone and hydrocortisone are currently in short supply in the United States, the options are oral formulations or intravenous dexamethasone.

SARS has created international anxiety because of its novelty, communicability, and rapid spread through jet travel and because it has caused illness in a large proportion of exposed medical and nursing personnel. We simply do not know where we are on the epidemic curve. Some fear is rational, but the 4.9 percent mortality rate is in fact similar to that seen generally with community-acquired pneumonia in the United States. Furthermore, the total number of deaths remains a small fraction of the estimated 35,000 deaths from influenza each year in the United States alone.

As the epidemic unfolds, praise is due to the hundreds of health care workers throughout the world who come to work every day to assist patients with SARS despite some risks to their own health. Such dedication defines the best traditions of our profession.

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## SARS-Associated Coronavirus

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The discovery that a novel coronavirus is the probable cause of the newly recognized severe acute respiratory syndrome (SARS), reported by Ksiazek et al. (pages 1953–1966), Drosten et al. (pages 1967–