

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, http://www.cdc.gov/ncidod/sars/specimens.htm)
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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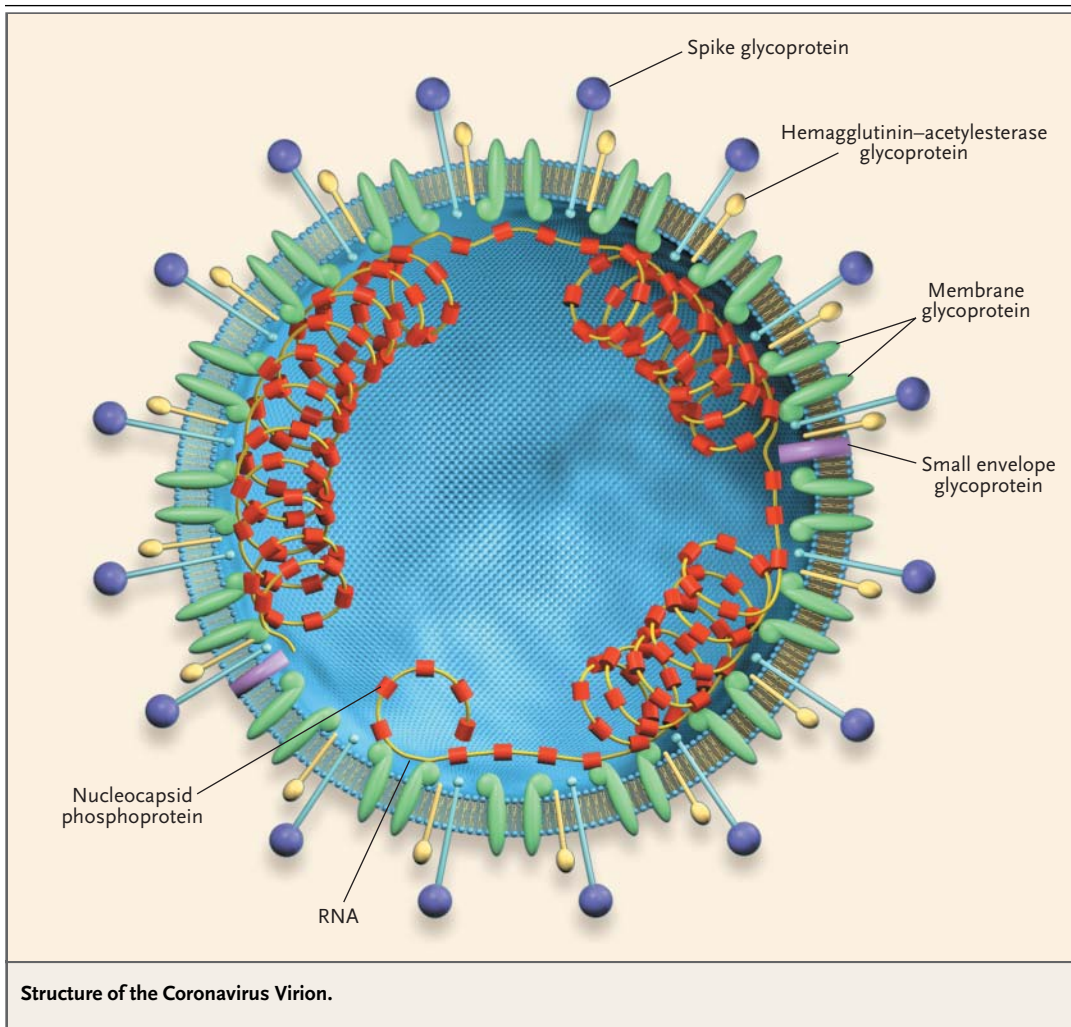
The discovery that a novel coronavirus is the probable cause of the newly recognized severe acute respiratory syndrome (SARS), reported by Ksiazek et al. (pages 1953–1966), Drosten et al. (pages 1967–

1976), and Peiris et al.¹ provides a dramatic example of an emerging coronavirus disease in humans, described by Poutanen et al. (pages 1995–2005), Tsang et al. (pages 1977–1985), and Lee et al. (pages 1986–1994). Although human coronaviruses cause up to 30 percent of colds, they rarely cause lower respiratory tract disease. In contrast, coronaviruses cause devastating epizootics of respiratory or enteric disease in livestock and poultry.

Most coronaviruses cause disease in only one host species. All known coronaviruses are found in three serologically unrelated groups. The Figure shows the structure of the virion. The message-sense RNA genome and the viral nucleocapsid phosphoprotein form a helical nucleocapsid. A corona of large, distinctive spikes in the envelope makes possible the identification of coronaviruses by electron microscopy. The spikes, oligomers

of the spike(S) glycoprotein, bind to receptors on host cells and fuse the viral envelope with host cell membranes. Coronaviruses in group 2 also have a hemagglutinin–acetyltransferase (HE) glycoprotein that binds to sugar moieties on cell membranes. Curiously, the gene for HE was apparently introduced into an ancestral coronavirus genome by recombination with the messenger RNA encoding HE of influenza C. The unique RNA-dependent RNA polymerase of coronaviruses often switches template strands during replication, causing RNA recombination when a cell is infected with several coronaviruses. This error-prone polymerase also generates point mutations and large deletions or insertions of foreign RNA into the viral genome.

The SARS-associated coronavirus could have arisen as a mutant of a human coronavirus that acquired new virulence factors, as a mutant of an an-



imal coronavirus that can infect human cells, or as a recombinant of two human coronaviruses or a human coronavirus and an animal coronavirus. Antibodies to the SARS-associated coronavirus were found in serum samples obtained from patients with SARS during convalescence but not in human serum samples banked before the SARS outbreak, suggesting that the SARS-associated coronavirus is new to the human population. The nucleotide sequence of the SARS-associated coronavirus genome (<http://www.bcgsc.ca/bioinfo/SARS>; <http://www.cdc.gov/ncidod/sars/sequence.htm>) differs substantially from sequences of all known coronaviruses.

Thus, the SARS-associated coronavirus is neither a mutant of any known coronavirus nor a recombinant of known coronaviruses. It is a previously unknown coronavirus, probably from a nonhuman host, that somehow acquired the ability to infect humans. Serologic tests of wild and domestic animals and birds in the region where the outbreak first appeared may identify the usual host. Comparison of isolates of the SARS-associated coronavirus from infected patients and from the natural host may reveal how the virus jumped to humans. In jumping to humans, did the SARS-associated coronavirus lose the ability to infect its original host? If there is no animal reservoir, there will be a better chance of eliminating the virus from humans.

The host range, tissue tropism, and virulence of animal coronaviruses can be changed by mutations in the S gene. The sequence of the S gene in the SARS-associated coronavirus may suggest how S glycoprotein affects the pathogenesis of SARS. The SARS-associated coronavirus genome sequence shows that it does not contain a gene encoding HE or large genes derived from another virus or host cell. It is an amazing feat that the SARS-associated coronavirus genome has been completely sequenced so quickly. The surprising discovery that the virus can be readily isolated in a monkey-kidney cell line was the key to the rapid molecular characterization of this novel coronavirus and the development of diagnostic tests for SARS. SARS-associated coronavirus has recently been proved to be the cause of SARS. Inoculation of monkeys with SARS-associated coronavirus from cell cultures caused lower respiratory tract disease, fulfilling Koch's postulate.

Both viral and host factors affect the virulence of coronavirus diseases in animals. The disease is usually most severe in neonates. The signs of infection

in immunosuppressed animals may differ from those in immunocompetent animals; immunosuppressed animals may also shed virus for prolonged periods and accumulate and possibly spread mutant viruses. The detection of SARS-associated coronavirus in fecal and serum samples from patients, as well as in respiratory specimens, suggests that this virus, like many animal coronaviruses, may be spread both by fecal contamination and by respiratory droplets. Host genes that affect the viral receptor, viral production, and immune responses to infection can determine the outcome of coronavirus infections, making certain species or strains of animals highly susceptible to lethal infection. For example, coronaviruses from domestic cats almost always cause death in cheetahs. Coinfection with other viruses, parasites, or bacteria exacerbates some animal coronavirus diseases. The deaths of 3 to 4 percent of patients with SARS may result from host factors that exacerbate the disease.

Although there are no approved drugs with proven efficacy against coronaviruses, there are potential targets for the development of new drugs. Protease inhibitors could prevent processing of the RNA polymerase or cleavage of the viral S glycoprotein. Inhibitors of coronavirus acetyltransferase activity might limit viral replication, as neuraminidase inhibitors inhibit the replication of influenzaviruses A and B. Inhibitors of membrane fusion might block viral entry, as do several new drugs against the human immunodeficiency virus. Antibodies against the viral S glycoprotein or the unidentified receptor for the SARS-associated coronavirus might also block entry of the virus.

Vaccines are available for some animal coronaviruses. Vaccination with live, attenuated virus is effective against porcine epidemic diarrhea virus and avian infectious bronchitis virus. However, recombination of genomes of vaccine strains with wild-type coronaviruses is a potential risk associated with using live, attenuated coronavirus vaccines in humans. Killed or subunit vaccines containing the spike glycoprotein, perhaps with other viral proteins, might prevent lower respiratory tract disease in humans. However, some vaccines against feline coronaviruses actually enhanced disease when vaccinated animals were exposed to wild-type virus, and antibody enhancement of disease is a potential risk of SARS vaccines in humans. It is possible that the current outbreak may be controlled and the virus eliminated by quarantine alone. Nevertheless, it is prudent to develop safe, effective drugs and vaccines

against the Urbani SARS-associated coronavirus as quickly as possible, in case the outbreak cannot be contained. The development of drugs and vaccines for SARS will also provide new strategies for the prevention and treatment of other coronavirus diseases of animals and humans.

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

SARS and Carlo Urbani

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On February 28, the Vietnam French Hospital of Hanoi, a private hospital of about 60 beds, contacted the Hanoi office of the World Health Organization (WHO). A patient had presented with an unusual influenza-like virus. Hospital officials suspected an avian influenzavirus and asked whether someone from the WHO could take a look. Dr. Carlo Urbani, a specialist in infectious diseases, answered that call. In a matter of weeks, he and five other health care professionals would be dead from a previously unknown pathogen.

We now know that Hanoi was experiencing an outbreak of severe acute respiratory syndrome (SARS). Dr. Urbani swiftly determined that the small private hospital was facing something unusual. For the next several days, he chose to work at the hospital, documenting findings, arranging for samples to be sent for testing, and reinforcing infection control. The hospital established an isolation ward that was kept under guard. Dr. Urbani worked directly with the medical staff of the hospital to strengthen morale and to keep fear in check as SARS revealed itself to be highly contagious and virulent. Of the first 60 patients with SARS, more than half were health care workers. At a certain moment, many of the staff members made the difficult decision to quarantine themselves. To protect their families and community, some health care workers put themselves at great personal risk, deciding to sleep in the hospital and effectively sealing themselves off from the outside world.

In some ways, the SARS outbreak in Hanoi is a story of what can go right, of public health's coming before politics. First-line health care providers quickly alerted the WHO of an atypical pneumonia. Dr. Urbani recognized the severity of the public health threat. Immediately, the WHO requested an

emergency meeting on Sunday, March 9, with the Vice Minister of Health of Vietnam. Dr. Urbani's temperament and intuition and the strong trust he had built with Vietnamese authorities were critical at this juncture. The four-hour discussion led the government to take the extraordinary steps of quarantining the Vietnam French Hospital, introducing new infection-control procedures in other hospitals, and issuing an international appeal for expert assistance. Additional specialists from the WHO and the Centers for Disease Control and Prevention (CDC) arrived on the scene, and Médecins sans Frontières (MSF, or Doctors without Borders) responded with staff members as well as infection-control suits and kits that were previously stocked for outbreaks of Ebola virus. The Vietnam French Hospital has been closed temporarily, and patients with SARS are cared for in two wards of the public Bach Mai Hospital, with the assistance of a team from MSF. No new cases in health care workers have been reported, and the outbreak in Vietnam appears to be contained. By dealing with the outbreak openly and decisively, Vietnam risked damage to its image and economy. If it had decided to take refuge in secrecy, however, the results might have been catastrophic.

Dr. Urbani would not survive to see the successes resulting from his early detection of SARS. On March 11, he began to have symptoms during a flight to Bangkok. On his arrival, he told a colleague from the CDC who greeted him at the airport not to approach him. They sat down at a distance from each other, in silence, waiting for an ambulance to assemble protective gear. He fought SARS for the next 18 days in a makeshift isolation room in a Bangkok hospital. Dr. Carlo Urbani died on March 29, 2003.