CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

SARS: Here to stay? Monkeypox: Beware of exotic pets

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ABSTRACT

Severe acute respiratory syndrome (SARS) is probably here to stay, and every health care institution should take precautions against an outbreak. The signs and symptoms of SARS are nonspecific, and there is no early diagnostic test, no specific treatment, and no vaccine. In some parts of the world, including Canada, more than 80% of probable cases were nosocomial.

KEY POINTS

Risk factors for adverse outcome include older age and hepatitis B surface antigen carriage.

The majority of SARS infections occurred in health care settings due to transmission of infection from unrecognized cases to health care workers, emphasizing the importance of having a high index of suspicion and using respiratory precautions in patients with suspected SARS.

When intensive infection control measures are necessary, as in the case of SARS, extended work shifts may lead to burnout of health care workers and should be avoided if possible.

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This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

ALTHOUGH THE RECENT OUTBREAK of severe acute respiratory syndrome (SARS) appears to have waned, most experts believe SARS is here to stay. This will be true especially if, as with influenza, there is an animal reservoir that cannot be eradicated.

SARS, unfortunately, is an infection control officer's nightmare: it has nonspecific signs and symptoms, no early diagnostic test, no specific treatment, and no vaccine forthcoming in the foreseeable future because the rate of mutation makes the SARS coronavirus a moving target.

An unsuspected SARS case with transmission to health care workers could shut down practically any health care system within days, resulting in an economic and public relations disaster.

The good news is that we have learned a tremendous amount about SARS in a short period of time and that the recent outbreak was controlled by aggressive infection control techniques. In the main portion of this article we review what we know about SARS so far. We also discuss the recent monkeypox outbreak.

EPIDEMIOLOGIC TRENDS: RAPID ONSET AND RAPID DECLINE

It seems as if there have been one or two new emerging infectious diseases each year, but until recently most of them have been previously recognized pathogens that have appeared in a new geographic area or affected a new population, such as West Nile virus. SARS, on the other hand, appears to be an entirely new pathogen that has found its way from animals into humans.

The worldwide epidemic curve of SARS cases shows rapid onset followed by rapid decline. SARS is not a pandemic, but

Revenge of the exotic pets: The US outbreak of monkeypox

The first outbreak of monkeypox in the Western Hemisphere began in the midwestern United States in May 2003, apparently having originated in a shipment of Gambian rats, intended for sale as pets. These unusual rats were shipped from Ghana to Texas on April 9, 2003, and apparently infected prairie dogs also for sale as pets. As of June 25, 2003, the US Centers for Disease Control and Prevention (CDC) had received reports on 79 suspected cases in six states.

This outbreak, which has since ceased, illustrates the hidden problem of exotic pets, and their potential for transmission of disease to humans. For instance, some experts believe that West Nile virus landed in the United States in a shipment of exotic birds, although that cannot be proven.

Shortly after the monkeypox outbreak, sales of prairie dogs and rodents imported from Africa were banned. Nonetheless, the sale of exotic pets is little regulated. For instance, the US Department of Agriculture has guidelines for pet importation, although the major component of that is rabies vaccination for dogs. The Fish and Wildlife Service monitors the sale of endangered species; still, many exotic animals can be found at numerous swap meets.

WHAT IS MONKEYPOX?

Monkeypox is a rare smallpox-like disease that primarily occurs in central and western Africa. The reservoir for the monkeypox virus in Africa is in squirrels, not monkeys, but the disease often kills monkeys that are primarily infected.

The CDC interim case definition of monkeypox, as of July 2, 2003, can be summarized as follows:[1]

- Rash with or without conjunctivitis
- Exposure to a suspected animal or human case
- Isolation of monkeypox in culture, or evidence on polymerase chain reaction testing, electron microscopy, or tissue staining.

A monkeypox rash is often visually indistinguishable from the rash associated with smallpox. Most US patients had a rash, fever, and/or respiratory symptoms, and many had lymphadenopathy, sweats, sore throat, chills, and/or headache. Lymphadenopathy is more common in monkeypox than in smallpox.

Just over half of the US monkeypox patients were female, and the median age was 26 years (range 4–53 years).[2] About one fourth were hospitalized, but most were discharged fairly quickly.[2] All patients had had either direct contact or a close association with ill prairie dogs or Gambian rats. In July 2003 the CDC recommended smallpox vaccination, as prophylaxis against monkeypox, for people who have had contact with infected animals or specimens and for health care workers and others who had recent close contact with monkeypox patients. Recommended infection control measures include hand hygiene after all contacts with the patient; gown, glove, and eye protection (if splash or spray is anticipated); respiratory protection (powered air purifying respirator or N95 filtering); and an isolation room with negative pressure to the surrounding area.

The case-fatality rate is 1% to 10% in African children with monkeypox, but a lower rate is expected in the Western Hemisphere because of superior living conditions. No one has died of monkeypox in the United States.

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between March 17 and July 11, 2003, 8,437 probable cases and 813 deaths were reported in 32 countries, according to the World Health Organization (WHO).[1] About two thirds of the cases and half of the deaths occurred in mainland China.

On June 24, 2003, the WHO lifted its recommendation against all but essential travel to Beijing, the last area in the world where this advice still applied,[2] and as of July 14, 2003, it stopped publishing a daily table of the cumulative number of reported SARS cases.[3]

In Canada, Singapore, and Hong Kong, more than 80% of the probable cases were associated with health care exposure. This highlights the risk of amplification of an unrecognized case of SARS in any hospital. Admission of a single patient, as the experience in Toronto has shown, can lead to secondary outbreaks and the need for intensive infection control efforts.

The reservoir for many respiratory diseases, such as respiratory syncytial virus and influenza, is in children. However, pediatric SARS cases have represented fewer than 2% of the total, even though it is certain that children have been exposed through kissing and other contact.[4] It is likely that some children have been infected without becoming clinically ill. The most notable difference when comparing clinical reports of pediatric SARS and the adult cases has been the absence of mortality in children.

Worldwide, the case-fatality rate for SARS is 10%, but as of July 11, 2003, no deaths had occurred among the 75 cases in the United States.[1] Age is a risk factor for poor outcome in patients who are hospitalized and admitted to an intensive care unit. In one analysis, the SARS-related mortality rate is 13.2% in people younger than 60 who are hospitalized vs 43% for people over age 60.[5]

HOW THE SARS CORONAVIRUS WAS DISCOVERED

Confirming Koch's postulates

Coronaviruses are so named because petal-shaped spike glycoproteins projecting from their surfaces look like a crown (corona). It has been known for some time that they can cause respiratory infections in humans and domestic animals, including pigs, mice, and birds, and that they tend to be species-specific.

Initially, though, there was some question about whether a coronavirus was causing SARS, because a human metapneumovirus (HMPv) was associated with some cases. Dutch investigators thus challenged macaque monkeys with clinical isolates of the putative SARS coronavirus with and without human metapneumovirus. The coronavirus caused an illness in the monkeys similar to the illness seen in humans, whereas there was no enhanced virulence with HMPv, and monkeys challenged with human metapneumovirus alone did not develop SARS. Autopsy studies detected the same pathology that was seen in humans, and Koch's postulates were confirmed in a relatively short period of time.

Nucleotide sequencing of the SARS coronavirus was completed shortly thereafter in multiple centers throughout the world and showed that the SARS coronavirus differs substantially from known coronaviruses. Therefore it has been postulated that it "jumped" from another species.

Virus structure

Coronaviruses are RNA viruses that fuse to host cell plasma membranes, completely away from the nucleus. RNA synthesis occurs in the endoplasmic reticulum and the Golgi complex. As with other RNA viruses, such as HIV, a high error rate in RNA polymerase during replication makes mutations common. Coronaviruses usually exhibit marked tissue tropism and typically infect only respiratory cells.

A SARS outbreak could shut down a hospital in days

Tracking the origin of SARS coronavirus: The food markets of Guangdong province

Investigations are ongoing concerning the location of the original cases of SARS. It is clear that in the Guangdong province of China, adjacent to Hong Kong, an outbreak of "pneumonia" occurred no later than November 2002. On February 11, 2003, the Chinese first reported cases of what they classified as "chlamydial pneumonia," and in March 2003 a secondary outbreak was reported in Hong Kong. On March 12, 2003, the WHO issued a global alert about cases of "atypical pneumonia."

In attempting to trace SARS to the original host, it may be important to note that of the first 900 SARS patients in China, 5% were food handlers and chefs. In China there are restaurants where customers choose their meal from animals enclosed in stacked cages, and in some cases, animal processing occurs in the kitchen. Antibodies to SARS-coronavirus have been found in the palm civet (related to the mongoose), which is a special ceremonial

dish in China, and in raccoon dogs and ferret badgers in Guangdong province. The rearing, slaughter, and preparation of these animals seems more likely to transmit the virus than ingestion. A seroprevalence study showed that 13% of wholesale workers dealing in exotic animals in Guangdong had antibodies to SARS coronavirus, which suggests that animal-to-human transmission is possible.

THE SARS DIASPORA

The first incubator appears to have been a hotel in Hong Kong, where a 64-year-old pulmonologist, in town for his nephew's wedding, stayed overnight on February 15, 2003. The next day he felt so ill that he went to a hospital in Hong Kong and told the house staff, "Put me in isolation. I've been taking care of some patients back in Guangdong with an unknown respiratory disease, some of whom have died." He was put in isolation but died on March 4, 2003.

There were no secondary cases in that hospital, but 12 hotel guests who stayed on the same floor as the physician became infected. Within the next few days, 9 of them left Hong Kong, which started the worldwide diaspora of SARS. A 78-year-old Canadian woman, who died in Toronto on March 5, 2003, was linked to all 140 subsequent cases in Toronto. An American businessman who died in Hanoi was linked to 22 cases in health care workers and 7 other cases in Hanoi. A Singapore woman who went to Hong Kong on a shopping trip with a friend recovered, but was linked to 90 subsequent cases at Tan Sock Seng Hospital in Singapore. In addition, her mother, father, and pastor died. A 26-year-old Hong Kong man recovered, but he was linked to 138 cases at Prince of Wales Hospital in Hong Kong, including 26 tertiary cases.

Mortality in SARS:
- **13% if < 60 years old**
- **43% if > 60**

How SARS spread: Hospitals and airplanes

Obviously, it is of great concern that hospitals became incubators for SARS. Not everyone will be an effective transmitter, but it is clear that, in the right setting, one person can infect well over 100 others. As might be expected, in the hospitals affected by SARS it was the nursing staffs that took the brunt of the illness.

Airplane travel certainly contributed to the diaspora of SARS. Known SARS patients have been on 35 flights, and transmission to a total of 16 passengers and crew members has been documented for 4 of those flights. "Peripatetic" is the term that epidemiologists use for "acquiring infection in one part of the country or world, but being diagnosed in another," and such cases clearly have occurred. Incidentally, the latest statistics indicate that there are 83 million visitors to China each year, including 1 million Americans, and 13 million visitors to Hong Kong, while at least 460,000 people travel from China to the United States. We really do live in a "global village."

Person-to-person transmission on airplanes has usually occurred within two rows of seats, supporting the idea that SARS is transmitted by droplets rather than through the air, as in the case of tuberculosis. Even so, the WHO and the Centers for Disease Control and Prevention (CDC) still recommend that medical personnel use respirators.

CLINICAL FINDINGS NO HELP IN MAKING THE DIAGNOSIS

The CDC's interim clinical case definition of SARS, last revised on July 18, 2003 (**TABLE 1**),[6] will probably not help a physician make the diagnosis, because the symptoms described could exist in half of the patients in the waiting room of a typical family practice.

Symptoms

According to a report on 138 cases of SARS at Prince of Wales Hospital in Hong Kong,[7] fever, chills or rigors, myalgia, cough, and headache were present in more than 50% of patients, but none of these symptoms is specific or pathognomonic. Neutropenia was noted in 34% of those patients, lymphopenia in 70%, and thrombocytopenia in 45%. Lactate dehydrogenase levels were elevated in 71%, but again, this is not specific. The incubation period was 3 to 10 days.

In another study[8] of 75 patients in Hong Kong, all treated with ribavirin and corticosteroids, fever and pneumonia initially improved in nearly all of these individuals, yet 85% developed recurrent fever after a mean of

9 days. Seventy-three percent, although they had diarrhea at the outset that improved, went on to develop recurrent diarrhea a week into the illness. Eighty percent had worsening of the chest radiograph after a week, and the respiratory symptoms worsened in nearly half of these individuals after a mean of 9 days.

This suggests that SARS is, in fact, a biphasic illness in which patients at the outset may get better, but then down the line get worse. The question is whether this represents the natural history of the illness, or whether this biphasic pattern is related to the use of corticosteroids in these patients. The investigators felt quite strongly that this was the natural history and not a function of the corticosteroids, but the jury is likely still out on this particular issue.

In a subset of patients evaluated in this study, viral shedding was common in blood, sputum, urine, and stool, and persisted for up to a month.

Pathology

Pathologists in Hong Kong report proliferation of epithelial cells, macrophages, and giant cells in the lungs of SARS patients, all nonspecific findings.[9] SARS has to be diagnosed based in part on the epidemiologic criteria.

Pulmonary presentation

The pathogenesis of severe SARS is diffuse alveolar damage with acute respiratory distress syndrome (ARDS). Twenty percent of chest radiographs are normal at the onset of infection; those that are not show airspace shadowing, focal or patchy consolidation, and ground-glass opacities.

The radiographic appearance of infiltrates in SARS can be highly variable, and can include peripheral, lobar, or wedge-shaped infiltrates, but more characteristically interstitial infiltrates that are bilateral in about 70% of individuals and may have a ground-glass appearance or may mimic ARDS on both chest radiography and computed tomography.

Risk factors for adverse outcome

One of the Hong Kong studies[8] found that 12% of the 75 patients surprisingly developed pneumomediastinum. Twenty percent went on to develop ARDS during the third week; 7% of patients in this particular study died.

This study also looked at risk factors associated with adverse outcome, and the independent risk factors that predicted the subsequent development of ARDS included age, such that for those between ages 61 and 80 the adjusted odds ratio was 28 for the subsequent development of ARDS. Another risk factor for the development of ARDS was the presence of hepatitis B surface antigen carriage. Some investigators have treated these patients with lamivudine, especially if they had received corticosteroids.

TABLE 1

CDC interim clinical case definition of SARS

Clinical criteria

- Asymptomatic or mild respiratory illness
- Moderate respiratory illness
  - Temperature > 100.4°F (38°C), and
  - One or more clinical findings of respiratory illness (eg, cough, shortness of breath, difficulty breathing, or hypoxia)
- Severe respiratory illness
  - Temperature > 100.4°F (38°C), and
  - One or more clinical findings of respiratory illness (eg, 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

Epidemiologic criteria

- Travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or previously documented or suspected community transmission of SARS, or
- Close contact within 10 days of onset of symptoms with a person known or suspected to have SARS

FROM US CENTERS FOR DISEASE CONTROL AND PREVENTION. UPDATED INTERIM U.S. CASE DEFINITION FOR SEVERE ACUTE RESPIRATORY SYNDROME (SARS). JULY 18, 2003. AVAILABLE AT: **WWW.CDC.GOV/NCIDOD/SARS/CASEDEFINITION.HTM.** CURRENT AS OF JULY 28, 2003.

SARS patients may initially improve, then get worse

Problems in detecting the virus

There are serious limitations in detecting SARS coronavirus in clinical specimens. According to one report, nasopharyngeal swabs were positive by reverse transcriptase polymerase chain reaction (RT-PCR) in only 32% of 75 patients at initial presentation, an average of 3.2 days after onset of illness.[8]

In that study the mean time to seroconversion, as assessed by enzyme-linked immunosorbent assay (ELISA), was 20 days.

However, the seroconversion rate at 1 month was still only 93%; at 21 days between 60% and 70% of patients had seroconverted. This observation should give one pause about excluding the diagnosis in at-risk individuals who remain seronegative at 21 days. The caveat is that all patients in this study were treated with corticosteroids, which may have delayed or impaired seroconversion.

The expense of laboratory testing is also an issue. The first commercially available RT-PCR test for SARS, introduced by Focus Technologies (Herndon, Va), costs $298.

TREATMENT PROTOCOLS: NO DATA

There is much speculation concerning the appropriate treatment for SARS. Therapies tried so far have included ribavirin and corticosteroids, and passive immunization with IgG antibodies to SARS Co-V (harvested from survivors). Coronavirus acetylesterase inhibitors and membrane fusion inhibitors are candidate agents for future investigation.

A protocol strongly advocated early in the outbreak by a group in Hong Kong consists of empiric antibacterial therapy plus ribavirin (400 mg every 8 hours intravenously for 3 days, then 1,200 mg twice a day for a total of 10 to 14 days) plus corticosteroids (methylprednisolone 3 mg/kg/day for 5 days, tapered over 21 days, or pulsed methylprednisolone for clinical relapse).[10] This group did not conduct a controlled trial, as they considered it unethical, and the protocol was finalized based on experience with the first 11 patients.

21 days may not be long enough for SARS seroconversion

INFECTION CONTROL

Isolation and quarantine also probably helped contain SARS in many communities. In infection-control parlance, the term "isolation" usually applies to hospitalized individuals who have tested positive for a disease or are strongly suspected of having it, whereas "quarantine" applies to asymptomatic contacts.

Care needs to be taken in the application of quarantine because it can be "leaky" and drive people underground. People may be reluctant to be identified as "SARS contacts" if they believe their liberties may be compromised. Travelers returning from an area with community transmission of SARS should not be put into isolation or quarantine unless they have been clinically assessed to have signs and symptoms of SARS.

What happens if a SARS patient is not quarantined

The results of a mathematical modeling analysis suggest that one individual with SARS who is not put into isolation or quarantine will infect three other people, on average.[11] For natural smallpox, the number is about 14, so SARS is not as contagious as some diseases, but three secondary cases still represents a substantial problem.

New standards may evolve, but our current infection control protocol for suspected SARS cases is as follows:

- Screening of patients in ambulatory clinics and those admitted to medical ICUs for adult respiratory distress syndrome and/or unexplained respiratory illness
- Airborne and contact precautions (eye protection, N95 respirators, and gowns)
- No special requirements for linen/food trays or decontamination of equipment
- Enhanced hand hygiene
- Travel advisory for all health care workers.

Are respiratory protection, double-gowning, and double-gloving necessary?

A recent report looking at the Canadian experience[12] suggests that fit-testing of respirators may have been helpful in preventing some cases of SARS in health care workers. The report follows the transmission of SARS from three patients to their treating clinician, who subsequently transmitted SARS to other heath care workers who treated the infected physician. Possible causes of transmission to the health care workers included the lack of formal respirator training and workers not being fit-tested.

In Toronto, *some* hospital personnel used full-face shields with two pairs of gloves and two layers of disposable gowns. It is thought that these practices might have helped contain SARS transmission, but they also caused stress and fatigue for health care workers, who were already working 18-hour shifts in some instances. When such intensive infection control measures are necessary, it may be wise

to go to shorter, more frequent shifts to give workers a respite. One may wonder about the need for double-gloving and double-gowning if SARS is transmitted via droplets. Although it is known that droplet transmission occurs, there are other potential avenues of transmission, such as fecal and oral routes. Another issue is that even health care workers who were adhering to infection control recommendations have become infected and died. Until more data become available, conservative measures such as double-gowning and double-gloving may be warranted.

According to epidemiologists, a region is free of a disease when no new cases have been identified during a period equal to twice the duration of the longest incubation period. For SARS, that means two times 10 days, or 20 days.

PREPARING FOR THE FUTURE

In Toronto, elective procedures were canceled, visitors were turned away, health care workers with fever after SARS exposure were quarantined at home for 10 days, and there was an exodus of patients and health care workers due to anxiety. An important lesson from the Canadian experience is that an institution's preparation for an outbreak of SARS must be a continuous process that examines the capacity to react, respond, and recover. There will need to be coordination through the hospital emergency incident commander and careful plans for proactive communication.

In terms of future research into SARS, some issues to be addressed are:

- Why are there "superspreaders" of SARS coronavirus—why do some people infect 150 others and some infect 9?
- Has SARS coronavirus mutated? Is it more virulent in some areas of the country or the world than others?
- What is the role of enteric spread? (A focal outbreak in an apartment complex in China seems to have been related to leaky sewage pipes, and SARS coronavirus was detectable in stool in 97% of patients by day 14).[9]
- To what extent does transmission depend on disease stage?
- What body fluids are significant in transmission?
- How widespread is SARS coronavirus among wild or farmed animals? Is there animal-to-animal transmission? Can animals harbor the virus without being sick? Can infected animals produce the virus long enough to infect humans directly?

A final lesson of the SARS outbreak is the importance of immediate real-time information disseminated through the Internet and the media in the recognition and control of emerging infectious diseases. New knowledge about the outbreak was available to physicians across the globe via the Internet. For physicians to remain current in the future as emerging infectious diseases are recognized will require use of the information highway rather than reliance on hard-copy medical journals.

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