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CHAPTER 17

Severe Acute Respiratory Syndrome: What Have We Learned

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EPIDEMIOLOGY

An outbreak of atypical pneumonia was noted in the Guangdong Province of southern China in the fall of 2002. The pneumonia was highly contagious and affected those who had been in close contact with the patients, such as health care workers and family members of the patients. The etiologic agent of this atypical pneumonia was not identified initially, and in many patients, their chest condition rapidly deteriorated and resulted in death.[1] In late February 2003, the Centers for Disease Control and Prevention termed this condition *severe acute respiratory syndrome* (SARS).[1]

In Hong Kong, SARS was first seen in a tourist from southern China. He was a medical doctor who had been taking care of patients with atypical pneumonia in Guangzhou and had had symptoms of a respiratory tract infection for 1 week before checking into a hotel in Hong Kong. This 64-year-old physician died from his chest infection 2 weeks later. Those other hotel guests staying on the same floor as this medical doctor, as well as their visitors, contracted the disease through social contacts. When the visitors returned to their residences in Hong Kong, they brought with them the disease, which led to its dissemination. Other guests staying at the hotel in Hong

Kong—an American–Chinese businessman who flew to Hanoi, Vietnam, 3 Singaporeans, and 2 Canadians—returned home, which then led to the outbreaks of SARS in Vietnam, Singapore, and Canada.[2]

The 2 Canadians who returned to Toronto infected another 6 individuals. Four of the infected individuals were from the same household, and the other 2 were infected while seeking medical treatment at the hospital where other patients were treated: 1 at an outpatient clinic and 1 at the emergency department.[3] Contact tracing of 21 Germans who had stayed in this hotel during this period was carried out, and 1 of them showed laboratory evidence of SARS. Thus, environmental contamination should be considered as a possible source of infection.[4] By early June 2003, the total number of patients affected globally was 8384, and of these, 770 had died.[5]

CLINICAL FEATURES

For a patient who has contracted SARS, the incubation period ranges from 2 to 16 days; the median incubation period is 6 days. More than 99% of patients presented with a persistent fever of 38°C or higher, and approximately 70% had associated chills and rigor. A nonproductive cough was noted in 70% of patients, and approximately 50% of patients complained of myalgia and dyspnea.[6] Less common symptoms included headaches, sputum production, sore throats, nausea and vomiting, and diarrhea.[7] Physical examination of the chest shows inspiratory crepitus and percussion dullness, most of which is located in the base of the lungs.[1] As in all types of atypical pneumonia, the respiratory symptoms and clinical features of SARS are disproportionately mild compared with the findings of imaging studies. Indeed, less than 25% of patients with atypical pneumonia had upper respiratory tract symptoms; gastrointestinal symptoms such as vomiting and diarrhea were present in 10% of patients.[8]

Common laboratory features included elevated lactate dehydrogenase levels in about 70% of patients; lymphopenia, thrombocytopenia and hypocalcemia were found in approximately 50% of the patients.[6,7]

CAUSATIVE AGENT

The identification of the etiologic organism among the conventional pathogens from patients with SARS was not successful initially. Eventually, a virus belonging to the family Coronaviridae was isolated from a lung biopsy specimen and from a nasopharyngeal aspirate. Subsequent investigations found that patients with SARS

showed a serologic response to this virus.[8] The family Coronaviridae includes the genus Coronavirus and Torovirus. Both of these are RNA viruses that are known to cause a variety of diseases in human beings and animals. A major cause of the common cold is related to the Coronavirus: types 229E and OC43.[9] These viruses occasionally are responsible for causing pneumonia in neonates or in elderly, debilitated, or immunocompromised patients. Some animal coronaviruses such as the avian infectious bronchitis virus might cause respiratory, gastrointestinal, or neurologic diseases.[10] Using the reverse transcription-polymerase chain reaction technique (RT-PCR), investigators first identified the sequence of a polymerase gene from a Coronavirus in the nasopharyngeal aspirate of 1 patient.[8] With the use of similar techniques, the isolation and identification of segments of this viral RNA were also confirmed from the throat swabs of patients with SARS.[11] The genome of the SARS-associated Coronavirus has now been sequenced, and this might be useful in the development of an antiviral agent or vaccine.[12]

DIAGNOSTIC CRITERIA

Imaging studies for patients with SARS complements the clinical diagnosis. Chest radiographs show a ground-glass appearance in the early phase of the infection, which rapidly progresses to focal or diffuse patchy involvement of the lung field (Fig 1). Unilateral pulmonary consolidation is common in the early phase, although many of them extend bilaterally when the infection becomes more advanced. The radiographic opacities were most evident at 8 to 10 days after the onset of clinical symptoms.[13] High-resolution computed tomography may show focal or patchy consolidation before the abnormalities are seen on chest radiographs (Fig 2).

The definition developed by the World Health Organization for the diagnosis of SARS was broadly inclusive and nonspecific (Table 1).[14] With the identification of the new Coronavirus[15,16] and the rapid sequencing of its genome,[12,17] new molecular assays were developed for diagnosis. These included RT-PCR tests targeting the polymerase gene of the virus and serologic tests using the enzyme-linked immunosorbent assay and immunofluorescent assay to detect the SARS-associated Coronavirus antibodies. The RT-PCR test is sensitive when specimens collected from the lower respiratory tract or stool are used. Serologic tests are reliable when patients show a rising titer, although the seroconversion time lag may be long in some patients.[18] Future research along this line should be directed at the development of a more sensitive test that would detect alter-

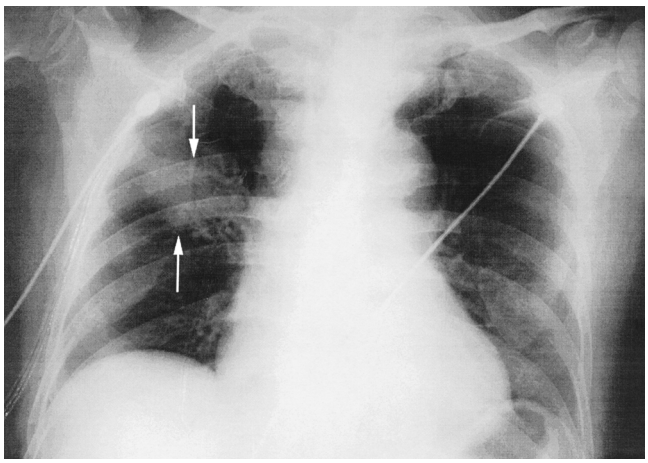

FIGURE 1.
Chest x-ray film: There is focal consolidation in the right upper zone *(arrows)*, which is an early feature in atypical pneumonia related to Coronavirus infection.

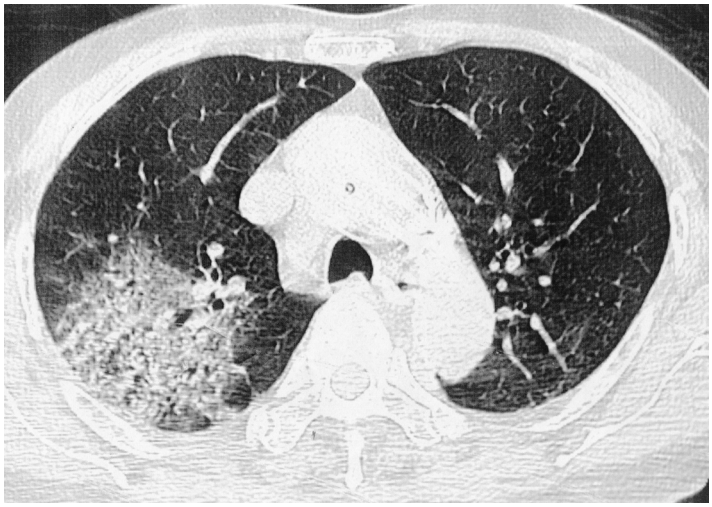

FIGURE 2.
High-resolution computed tomography: An area of ground-glass opacification with superimposed reticulation noted in the posterior segment of the right upper lobe is another feature of atypical pneumonia that is part of the manifestation of severe acute respiratory syndrome.

TABLE 1.
World Health Organization Case Definition for Suspected and Probable Severe Acute Respiratory Syndrome (SARS)

Suspected case
- Any patient with a fever > 38°C (104°F) *and*
- One or more symptoms of a lower respiratory tract illness, such as a cough, difficulty in breathing, or shortness of breath *and*
- Having had close contact with an individual believed to have SARS or to have traveled to a region where there has been documented transmission of the disease *and*
- No alternative diagnosis can fully explain the illness.

Probable case
- An individual meeting the criteria for a suspected case along with radiographic features of pneumonia or respiratory distress syndrome *or*
- An individual with an unexplained respiratory illness resulting in death whose autopsy results demonstrate the following pathologic feature: respiratory distress syndrome without an identifiable cause.

nate target genes such as the nucleocapsid gene, which is more abundant than the replicase gene of the virus.[19]

ROUTE OF TRANSMISSION

Studies have identified coronaviruses genetically similar to those responsible for the SARS infection in a number of animal species indigenous to the southern part of China and parts of Southeast Asia. These are the masked palm civet and the raccoon dog. Another animal, the Chinese ferret badger, also has antibodies against the SARS Coronavirus. These animals are traditionally considered to be delicacies for human consumption in markets throughout southern China.[20] The infection initially affected those individuals handling, slaughtering, and selling these animals as food or those individuals preparing the animals and serving them as food. The transmission of the viral particles leading to SARS infection in patients occurred first through aerosols and droplets from respiratory secretions[21] and second through contamination of inanimate materials or objects by infectious respiratory secretions or body fluids such as feces, urine, saliva, and tears.[22]

The Coronavirus survives for 4 days in diarrheal stool and at least for 2 days on plastic surfaces at room temperature. It survives for less than 30 minutes in a cultural medium at 56°C and for less than 5 minutes in formaldehyde and 75% ethanol.[23]

MANAGEMENT

As a newly emerging infectious disease, SARS is highly contagious and, on infection of an individual, leads to significant morbidity and mortality. The route of infection is through the mucosal membranes or conjunctiva. The mode of spreading is through direct contact of the virus, which is believed to be transported via aerosol and fine droplets. This has posed a significant threat to medical and nursing staff caring for these patients, especially when the patients are receiving ventilatory support, in which frequent suctioning to remove bronchial secretions is mandatory. The first index patient in Hong Kong was admitted on February 22, 2003. By April 18, 2003, the total number of clinically confirmed patients with SARS in Hong Kong was 1523, of whom 316 (20.7%) were health care workers, including medical doctors, nurses, and hospital ward attendants. The overall mortality rate was about 15%, and it was 3 times higher among patients who had an associated chronic illness.

Postmortem examination of patients who died of SARS showed that most had diffuse alveolar damage affecting the lungs. The morphological changes identified included bronchial epithelial denudation, loss of cilia, and squamous metaplasia. The increased presence of macrophages and hemaphagocytosis suggests that cytokine dysregulation was responsible for the clinical picture.[24] The therapeutic regimens developed included the combined use of an antiviral agent, ribavirin, and pulsed methylprednisolone. More than 50% of patients showed a rapid and sustained response, and 45% showed steady improvement with these management strategies.[25] With this treatment regimen, the associated morbidity was acceptable, and the patient mortality rate was markedly reduced.

PREVENTIVE MEASURES

It has been reported that viral DNA is present in the aerosol generated by CO_2 lasers used to treat papillomavirus-infected verrucae.[26] Recent studies[27] have shown that these viral particles are infective and may be responsible for the transmission of disease. Thus, generation of aerosol should be reduced to a minimum during the care of patients with SARS so that transmission of the Coronavirus can be prevented. The size of aerosols considered to carry particles in a hospital environment is 0.3 to 0.5 μm,[28] and filters used to trap particles in the plume generated by laser therapy are 0.22 μm.[29] For health care workers taking care of patients with SARS, one piece of personal protective equipment is the N95 mask, which will filter 95% of particles 0.1 to 0.3 μm.[30]

The effort to reduce the spread of disease through direct contact or droplet contact in hospitals managing these patients involved generating, implementing, and enforcing a series of guidelines.[31] These included the identification and reporting of affected patients, dissemination of information to the public, enforcement of infection control measures, development of diagnostic tests, evaluation of therapeutic regimens, and the coordination of clinical services. These measures are primarily directed at tracing and isolating the contact of patients as soon as possible before they spread the virus further.[32]

The various measures used to prevent transmission of infection by direct contact include the use of gloves, surgical masks, gowns, goggles, N95 masks, face shields, and total body coverings such as Barrier Man suits. The choice of personal protective equipment has to balance the need for adequate protection with the need to easily move and carry out various procedures during patient care. Wearing masks, gowns, and gloves and frequent washing of hands were adequate in significantly reducing the risk of cross-infection during the care of patients with SARS.[33]

Overall, about 20% of patients infected with SARS require endotracheal intubation and ventilatory support during the course of the disease; the risk of disease transmission at the time of intubation is quite significant.[34] Necessary precautions must be taken when caring for these patients who require the use of a ventilator. The risk of being infected with SARS when carrying out surgical procedures such as tracheostomies or other emergency operations for infected patients is high. Measures should be taken to reduce the risk of transmission during surgery.

PRECAUTIONARY MEASURES TO ELIMINATE TRANSMISSION OF CORONAVIRUS

WARDS AND INTENSIVE CARE UNITS DESIGNATED FOR PATIENTS WITH SEVERE ACUTE RESPIRATORY SYNDROME

In the wards and intensive care units (ICUs) designated for the management of patients with SARS or suspected SARS, space must be adequate between beds to reduce the chance of direct or indirect contact. If possible, a screen should be placed between the beds. This will reduce the transmission of the Coronavirus and the spread of disease.

Airflow in these wards and ICUs should have a negative pressure gradient, that is, the current of air flow should be directed from the outside to the interior of the rooms, thus reducing the transmis-

sion of droplets to other areas in the hospital. A designated air outlet should be constructed to release air from the ward or ICU to an uninhabited space within the hospital compound. Nursing staff should wear water impermeable caps, gowns, and goggles and should wash hands frequently. Gloves should be worn only when carrying out an assigned procedure and should be removed when the procedure is completed. All personal protective equipment should be disposed of properly after it has been used.

When a patient needs ventilatory support in the ICU, suction of the tracheobronchial tree should be carried out with a closed suction system. Viral filters should be placed at the exhaust end of the ventilator system to prevent the dissemination of infected material to the rest of the system.

OPERATING ROOM

A separate operating suite should be designated for patients with SARS or suspected SARS so that transmission of the infection to other patients who need an operative procedure can be avoided. The ventilation system of the operating room should also have a negative pressure gradient so that a controlled flow of air is allowed into the operating room from outside and is then directed to a designated exhaust, which will reduce the transmission of droplets to health care workers in the operating room.

Surgeons carrying out an operation on a patient with SARS are advised to wear caps, N95 masks, goggles, gowns, gloves, and face shields. At the completion of the surgical procedure, this protective equipment should be removed gently and smoothly in the reverse order of how it was put on. Careful removal of personal protective equipment is essential; otherwise, surgeons might contaminate themselves with the virus found on the outside of this protective equipment during the removal process.

INSTRUMENTS AND EQUIPMENT

The use of equipment that produces aerosols or droplets should be limited, as it might contribute to the spread of the virus. This kind of equipment includes nebulizers, suction devices, and flexible endoscopes used for the examination of the upper aerodigestive tract.

Nebulizers should not be used at all, and the use of suction devices should be limited; if necessary, a closed suction system device should be used. Viral filters should be used whenever applicable so that the chance of spreading droplets and viral particles is reduced. Endoscopic examinations, in particular nasopharyngoscopy and bronchoscopy, should be performed only when absolutely necessary because the instruments used in these procedures have suction

systems that produce aerosols that could contribute to the spread of the virus.

ENDOTRACHEAL INTUBATION

Endotracheal intubation of a patient with SARS is risky for health care workers.[21] The physician and nursing staff should wear full protective equipment: caps, N95 masks, goggles, gowns, gloves, and face shields. Patients should receive adequate oxygen before being completely paralyzed and immobilized at the time of endotracheal intubation. The use of suction devices should be minimized, and viral filters should be used whenever applicable. Flexible bronchoscope-assisted intubation is not advisable.

GENERAL GUIDELINES ON SURGICAL AIRWAY MANAGEMENT IN PATIENTS WITH SEVERE ACUTE RESPIRATORY SYNDROME

The surgeon contributes to airway management in the following 3 circumstances:

1. Perform a tracheostomy for patients with SARS in need of a ventilator
2. When on standby for an expectedly difficult intubation in a patient with SARS
3. When attending a failed emergency intubation in a patient with SARS

When indicated in a patient who is receiving mechanical ventilation, a surgical airway should ideally be done as an elective tracheostomy. For an expectedly difficult intubation, a surgeon should be on standby in readiness for immediate intervention if needed. In the case of failed attempts at emergency intubation, the surgeon is called on for urgent surgical airway insertion.[35]

The staff of the tracheostomy team should include 1 surgeon, 1 intensivist or anesthetist, and 1 standby staff member, either a physician or a nurse. Every member of the team should wear full personal protective equipment, including a cap, an N95 mask, goggles, a gown, gloves, and a face shield. Surgeons should wear an additional pair of gloves and surgical boots. They should also wear 1 disposable, water-impermeable surgical gown next to the body and a second water-impermeable gown externally.

PROCEDURES FOR A SAFE TRACHEOSTOMY

The patient should receive adequate oxygenation before the procedure and then should be completely paralyzed to abolish any movement, especially reflex coughing during the incision on the trachea and during the insertion of the tracheotomy tube.

All forms of assisted ventilation must be stopped before the tracheotomy.

Open suction for tracheal secretions should not be used, and diathermy should be used sparingly. Jet ventilation is prohibited under these circumstances.

In case of a failed endotracheal intubation, either electively or under emergency conditions, manual ventilation with a tight mask is given until the patient has attained adequate oxygenation. The surgeon can then decide on either a cricothyroidotomy or a tracheostomy.

EPILOGUE

Caused by the Coronavirus, SARS was a new disease in early 2003; initially, there was much controversy concerning the diagnosis, patient management, and isolation strategies. In Hong Kong, the total number of patients who were admitted to hospitals because of SARS was 1755, and 299 of them died of the disease. Among those who died, 8 were health care workers; these included 4 physicians, 1 nurse, and 3 other hospital support staff. After the epidemic, 3 official inquiries were carried out by the government and related authorities. These have led to the resignations of the Secretary for Health, Welfare, and Food and the Chairman of the Hospital Authority, who are responsible for the management of public hospitals in Hong Kong. During the epidemic, the people of Hong Kong became acutely aware of public heath, the hygienic status of their living environment, and the importance of the nature and devastation of this infectious disease. This alertness has continued to the present and has helped to make Hong Kong a much healthier city.

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