

CE update [microbiology]

# Severe Acute Respiratory Syndrome Epidemiology and Control

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After reading this article, the reader should understand the epidemiology of SARS along with preventive measures that laboratory professionals can take.

**Chemistry exam 70401** questions and corresponding answer form are located after the “Your Lab Focus” section on p. 121.

- ▶ Severe acute respiratory syndrome (SARS) is a newly identified respiratory illness that has been reported in various locations around the world.
- ▶ Since its initial identification, probable cases of SARS have been reported in 30 countries and 2 administrative regions within China.
- ▶ Clinical studies have proven that a novel coronavirus is associated with the SARS outbreak and plays an etiological role in the illness.
- ▶ The genus coronavirus is comprised of a diverse group of large, enveloped, positive RNA-stranded viruses that cause respiratory and enteric diseases in humans as well as in animals.

Severe acute respiratory syndrome is a newly identified respiratory illness that has been reported in various locations around the world. The disease is believed to be caused by a virus from the family of coronaviruses, which is widely known for causing upper respiratory illnesses in the elderly.<sup>1</sup> The syndrome has its origin in the Guangdong Province of China from where it is believed to have spread to different parts of the globe.<sup>2</sup> The SARS epidemic has not only had a far reaching effect upon the international medical community but has had a heavy impact on the global economy. According to J. P. Morgan, SARS costs Canada more than \$30 million per day and is expected to cause Canada's national economic growth to drop by 1 percentage point for the year.<sup>3</sup> Another industry that has

suffered greatly due to SARS is tourism. Travel to Hong Kong, an area hit hard by the SARS epidemic, has decreased by more than 85%.<sup>4</sup> With strict epidemiological control, the epidemic appears to be subsiding. In fact, in early July, 2003, the World Health Organization announced that the initial global SARS outbreak had been contained.<sup>5</sup>

## Epidemiology

The first case of SARS was identified in mid-November 2002 in South-eastern China.<sup>2</sup> In February 2003, Carlo Urbani, an Italian epidemiologist at the World Health Organization's office in Hanoi, Vietnam, was the first physician to discover that this dangerous new microbe was beginning to spread around the globe.<sup>6</sup> Since its initial identification, probable cases of SARS have been reported in 30 countries and 2 administrative regions within China.<sup>7</sup> The global case-fatality rate for probable SARS is 9.6%. Preliminary research indicates that SARS primarily occurs in adults and the elderly and seems to be far less likely to occur in children.<sup>2</sup>

The People's Republic of China has had the largest number of reported probable cases of SARS and is considered the heart of the epidemic.<sup>7</sup> The peak of the SARS epidemic in China occurred on April 21, 2003 when 447 new probable cases of SARS were reported.<sup>8</sup>

Hong Kong has had the second largest number of cases of probable SARS with 1,755 and has had 298 SARS related deaths.<sup>7</sup> The most notable outbreak of SARS in Hong Kong

occurred at the Amoy Gardens apartment block where 321 cases developed. It is believed that the outbreak at the Amoy Gardens was caused by person-to-person contact via the use of shared communal facilities such as sewage lines, stairs, and elevators.<sup>9</sup>

The outbreak of SARS in Canada has largely been confined to Toronto, Ontario. The case-fatality ratio for SARS in Canada is 15.2%, which is higher than the global ratio of 9.6%. This elevated case-fatality ratio in Canada is due to the fact that the Canadian patients infected with SARS tend to be of older age and tend to have other chronic illnesses that in combination with SARS led to a fatal outcome.<sup>2</sup>

Singapore has had 206 probable cases of SARS and 32 deaths attributed to the disease.<sup>7</sup> The majority of infections in Singapore have been in hospital staff, inpatients, and those visiting the hospital.<sup>2</sup>

In the United States, 346 suspected cases of SARS have been reported from 42 states as well as Puerto Rico.<sup>10</sup> Seventy-five probable cases of SARS have also been identified with no deaths reported.<sup>7</sup> Nearly all probable cases of SARS in the United States have been attributed to individuals traveling to countries that have had SARS outbreaks.<sup>7</sup> There has been a very low transmission rate for SARS from patients to health care workers in the United States.<sup>2</sup> This can be attributed to greater awareness of SARS in the United States and superior procedures to prevent the transmission of the disease.

The transmission pattern for SARS seems to involve health care workers, patients, their family members, social

contacts, and international travelers. SARS appears to be spread most commonly by close person-to-person contact involving exposure to infectious droplets, and possibly by direct contact with infected body fluids.<sup>2</sup> Evidence from Singapore indicates that some infected persons may be super spreaders. In this particular case, 5 individuals were responsible for the spreading of SARS to 60% of the 206 cases in Singapore.<sup>11</sup>

### Symptoms

The World Health Organization definition for a suspect case of SARS is characterized by a patient temperature >100.4°F (>38°C), lower respiratory tract symptoms, and contact with a person believed to have had SARS or history of travel to an area of documented transmission.<sup>12</sup> A probable case of SARS is a suspected case that also includes chest radiographic findings of pneumonia, acute respiratory distress syndrome (ARDS), or an unexplained respiratory illness resulting in death with autopsy findings of ARDS without identifiable cause.<sup>12</sup> Positive laboratory results, which include detection of the antibody to the SARS virus as well as detection of SARS RNA via a RT-PCR test, are used to further reinforce a case being classified as probable.<sup>12</sup>

The average incubation period of SARS is usually 2 to 7 days but certain cases have been found to have incubation periods as long as 10 days.<sup>13</sup> The illness generally begins with a prodrome of fever greater than 38°C. The fever is often accompanied by feelings of malaise and myalgias as well as instances of chills, rigors, and headaches.<sup>14</sup> During this preliminary stage of the illness, some cases have exhibited mild respiratory symptoms.<sup>14</sup> However, these symptoms are not always present. Along with these symptoms during the early respiratory phase are elevated creatine phosphokinase levels (up to 3,000 IU/L) and hepatic transaminases (2- to 6-times the upper limits of normal). In most cases, gastrointestinal findings are absent, although a few patients have reported diarrhea during the febrile prodrome.<sup>15</sup>

After 3 to 7 days, lower respiratory symptoms emerge with the onset of a

dry, non-productive cough, dyspnea, and may be in conjunction with hypoxemia.<sup>14</sup> In 10% to 20% of reported cases, the respiratory symptoms require intubation and mechanical ventilation.<sup>14</sup> At the peak of the respiratory symptoms, approximately 50% of patients suffer from leukopenia and thrombocytopenia (50,000 to 150,000/ $\mu$ L).<sup>14</sup>

Chest radiographs may be clear of any signs of infiltrates during the febrile prodrome and may remain clear throughout the course of illness.<sup>14</sup> However, in a significant percentage of cases, the respiratory symptoms are characterized by early focal infiltrates progressing to more generalized, patchy, interstitial infiltrates.<sup>14</sup> Areas of consolidation have also been found in some chest radiographs in the later stages of SARS.<sup>14</sup>

### Cause

Clinical studies have proven that a novel coronavirus is associated with the SARS outbreak and plays an etiological role in the illness.<sup>16</sup> The genus coronavirus is comprised of a diverse group of large, enveloped, positive RNA-stranded

viruses that cause respiratory and enteric diseases in humans as well as animals.<sup>17</sup> A corona of large, distinctive spikes in the envelope makes possible the identification of coronaviruses by electron microscopy.<sup>17</sup> The spikes bind to receptors on host cells and fuse the viral envelope with host cell membranes. Coronavirus DNA has the largest genome of any known group of viruses with approximately 30,000 nucleotides.<sup>18</sup>

Although coronaviruses cause up to 30% of colds in humans, they are not known for causing major respiratory illnesses.<sup>17</sup> However, coronaviruses are known for causing devastating respiratory infections in livestock and poultry that are almost always fatal.<sup>17</sup> This information has lead researchers to believe that the SARS-associated coronavirus may have arisen as a mutant of a human coronavirus that obtained new virulence factors or as a recombinant of a human coronavirus and an animal coronavirus.<sup>17</sup> Researchers believe the probable animal hosts to be the masked ferret civet, raccoon dog, and Chinese

ferret badger.<sup>19</sup> It is still unclear at this time if humans contracted the virus from these animal hosts or vice versa.

The fact that antibodies to the SARS-associated coronavirus were found only in serum samples obtained from patients with SARS during their recovery period and not in human serum samples obtained prior to the SARS outbreak suggests that the SARS-associated coronavirus is new to the human population.<sup>17</sup> The nucleotide sequence of the SARS-associated coronavirus genome differs substantially from sequences of all known coronaviruses. Genetic characterization of the SARS-associated coronavirus indicates that the virus is only distantly related to any known coronaviruses. In fact, only 50% to 60% of the nucleotide sequence of the SARS-associated coronavirus is identical to known coronaviruses.<sup>20</sup> Thus, the SARS-associated coronavirus is a previously undocumented coronavirus.

### Diagnosis

Laboratory diagnosis of SARS is made by cell culture techniques, RT-PCR, and by serology. Viruses can be recovered from the nasopharynx, lungs, and feces using techniques such as bronchial alveolar lavage.<sup>21</sup> Viruses can also be found in blood, plasma, and serum samples. The antibody to SARS develops in 10 days and can be detected by indirect immunofluorescence technique.<sup>22</sup>

### Prevention

#### Exposure Management

The Centers for Disease Control (CDC) recommends the following guidelines to help clinicians manage persons who may have been exposed to SARS through international travel to an area with community transmission or as a result of a public health investigation. The CDC's recommendations are applicable for any country but are primarily intended for the United States.<sup>23</sup>

#### Quarantine

Persons who may have been exposed to SARS should have their temperature measured twice a day for fever and be checked for respiratory symptoms

during the 10 days following exposure. During this time, if neither fever nor respiratory symptoms arise, persons who may have been exposed to SARS need not limit their activities outside the home.

Exposed persons should notify their health-care provider immediately if fever or respiratory symptoms develop. Prior to clinical evaluation, health-care providers should be informed that the individual may have been exposed to SARS so proper arrangements can be made.

### Isolation

Symptomatic persons exposed to SARS should follow the following infection control precautions.

- If fever or respiratory symptoms develop, the person should limit interactions outside the home and continue to monitor temperature twice daily. In addition, the person should use infection control precautions (see below) in the home to minimize the risk for transmission.
- If symptoms improve within 72 hours after first symptom onset, the person may be allowed, after consultation with local public health authorities, to return to their normal activities.
- For persons who progress to meet the case definition for suspected SARS, infection control precautions should be continued until 10 days after the resolution of fever and the respiratory symptoms.
- If the illness does not progress to meet the case definition, but the individual has persistent fever or unresolved respiratory symptoms, infection control precautions should be continued for an additional 72 hours, at the end of which time a clinical evaluation should be performed. If the case definition is met, infection control precautions should be continued as described above. If case definition criteria are not met, infection control precautions can be discontinued after consultation with local public health authorities and the evaluating clinician.
- Persons who progress to meet the case definition for suspected SARS

or whose illness does not meet the case definition, but who have persistent fever or unresolved respiratory symptoms during the 72 hours following onset of symptoms should be tested for SARS coronavirus infection.

If a person exposed to SARS is symptomatic while outside of the home local public health authorities should be consulted regarding the need for education and follow-up of persons in attendance.

### Infection Control

#### Household Precautions

Due to the highly infectious nature of SARS, patients diagnosed with SARS pose a risk of transmission to close household contacts as well as health care personnel they come in contact with. In order to prevent further infections through household contact, the CDC has suggested the following infection control measures for patients with suspected SARS in households or residential settings.<sup>24</sup>

Patients with SARS should limit interactions outside the home until 10 days after the resolution of fever, and respiratory symptoms are either absent or improving. During this time, infection control precautions should be used. At this time, in the absence of fever or respiratory symptoms, household members or other close contacts of SARS patients need not limit their activities outside the home.

All members of a household with a SARS patient should wash hands frequently or use alcohol-based hand rubs, particularly after contact with body fluids. Use of disposable gloves should be employed for any direct contact with body fluids of a SARS patient. After activities involving contact with body fluids, gloves should be discarded and hands should be cleaned. Gloves must never be washed or reused.

Each patient with SARS should be advised to cover his/her mouth and nose with a facial tissue when coughing or sneezing. If possible, a SARS patient should wear a surgical mask during close contact. When a SARS patient is unable to wear a surgical mask, household

members should wear surgical masks when in close contact.

Sharing of items between SARS patients and others should be avoided. Environmental surfaces soiled by body fluids should be cleaned with a household disinfectant; gloves should be worn during this activity. Household waste soiled with body fluids of SARS patients, including facial tissues and surgical masks, may be discarded as normal waste.

Household members and other close contacts of SARS patients should be actively monitored by the local health department for illness. Household members or other close contacts of SARS patients should be vigilant for the development of fever or respiratory symptoms and, if these develop, should seek healthcare evaluation.

### Health-Care Setting Precautions

In order to prevent further transmission of SARS to health-care workers or others in health-care facilities, the World Health Organization has suggested that hospitals abide by the following infection control measures for patients diagnosed with SARS in their health-care settings.

**Outpatient/Triage Setting**<sup>25</sup>: Individuals who require assessment for SARS should be rapidly diverted by triage nurses to a separate area in order to minimize transmission opportunities to others. These patients should be given a facemask to wear as well as the staff involved in the triage process. The staff should wash hands before and after contact with any patient and after activities likely to cause contamination. Disinfectants such as fresh bleach solutions should be widely available at appropriate concentrations and should be used often in areas where patients are treated. Wherever possible, patients under investigation for SARS should be separated from the probable cases.

**Inpatient Setting**<sup>25</sup>: Probable SARS cases should be isolated and accommodated as follows in descending order of preference.

- Negative pressure rooms with the door closed.
- Single rooms with their own bathroom facilities.

- Cohort placement in an area with an independent air supply, exhaust system, and bathroom facilities.
- Turning off air conditioning and opening windows for good ventilation is recommended if an independent air supply is unfeasible.
- WHO advises strict adherence to the barrier nursing of patients with SARS, using precautions for airborne, droplet, and contact transmission.
- Particular attention should be paid to interventions such as the use of nebulisers, chest physiotherapy, bronchoscopy, or gastroscopy; any other interventions that may disrupt the respiratory tract or place the health care worker in close proximity to the patient and potentially infected secretions.
- Movement of patients outside of the isolation unit should be avoided. If moved the patients should wear a facemask.
- Visitors, if allowed by the health care facility, should be kept to a minimum. They should be issued personal protective equipment (PPE). The PPE worn in this situation should include: a facemask providing appropriate respiratory protection, a single pair of gloves, eye protection, a disposable gown, an apron, and footwear that can be decontaminated.
- Disposable equipment should be used wherever possible in the treatment of patients with SARS. If devices are to be reused, they should be sterilized in accordance with manufacturers' instructions. Surfaces should be cleaned with broad-spectrum disinfectants.
- Hand washing is crucial. Therefore, access to clean water is essential. Hands should be washed before and after contact with any patient and after activities likely to cause contamination.
- Linen from the patients should be prepared on site for the laundry staff. Appropriate PPE should be worn in this preparation and the linen should be put into biohazard bags.

### Cleaning and Disinfection

Cleaning and disinfection of surfaces is a vital component of routine infection control in health care facilities. Although environmental surfaces (eg, floors, table tops) are generally not involved in transmission of microorganisms, some surfaces, especially those that are touched frequently (eg, bed rails, door knobs, lavatory surfaces) may serve as important reservoirs of microbial contamination.<sup>26</sup> If these surfaces are touched, the microbial agents can be transferred from the surfaces to mouth, eyes, nose, or other places. Strict hand hygiene and a regular schedule of cleaning and disinfection will limit the microbial particles found in and around the patient's surroundings. Cleaning and disinfection is integral for controlling the spread of SARS in health care settings. The cleaning methods recommended by the CDC are as follows<sup>26</sup>:

- In-patient rooms housing SARS patients should be cleaned and disinfected daily and at the time of patient transfer or discharge.
- Daily cleaning and disinfection should include horizontal surfaces (eg, over-bed table, night stand), surfaces that are frequently touched by patients, and health care personnel (eg, bed rails, phone), and lavatory facilities.
- Terminal cleaning and disinfection following discharge should include the type of surfaces described above plus obviously soiled vertical surfaces, frequently touched surfaces (eg, light cords, switches, door knobs), and durable patient equipment (eg, bed, night stand, over-bed table, wheelchair, commode). Curtain dividers also should be changed and laundered as appropriate for the curtain fabric.
- Patient care equipment such as mechanical ventilators, pulse oximeters, and blood pressure cuffs, should be cleaned and disinfected in accordance with current CDC recommendations and manufacturer's instructions.

### Treatment

Current treatment recommendations for SARS involve treating the patient's symptoms (ie, intubation for

severe respiratory ailments) while allowing the disease to run its course.<sup>27</sup> At present, there are no approved drugs with proven efficacy against coronaviruses.<sup>28</sup>

Although no specific treatment recommendations for SARS have been made by the CDC or the WHO at this time, a vast amount of research is being conducted in search for a suitable treatment for SARS. Recent research has indicated that there are several avenues that pharmaceutical developers can take in their development of a SARS fighting drug. Protease inhibitors could impede the processing of the RNA polymerase or cleavage of the viral S glycoprotein.<sup>17</sup> Viral replication activity may be limited by inhibitors of coronavirus acetyltransferase, as is the case with neuraminidase inhibitors which inhibit the replication of influenza viruses A and B.<sup>17</sup> Viral entry may be blocked by inhibitors of membrane fusion similar to several new drugs developed to fight the human immunodeficiency virus.<sup>17</sup> Entry to the virus may also be blocked by antibodies against the viral S glycoprotein or the unidentified receptor for the SARS-associated coronavirus.<sup>17</sup>

Specific drugs and treatments that have been suggested for the treatment of SARS include: ribavirin, quercetin with vitamin C, as well as a blood serum from recovered SARS patients. Ribavirin is a synthetic nucleoside analog that has antiviral activity against RSV as well as influenza, parainfluenza, adenovirus, and herpes simplex viruses. The exact mechanism of action taken by ribavirin remains unknown. It is believed that ribavirin interferes with messenger RNA expression which results in the inhibition of viral protein synthesis. Ribavirin is administered by inhalation using a special small particle generator. Physicians in Hong Kong and Toronto have used ribavirin extensively as a treatment for SARS.<sup>18</sup> They believe that the drug plays a considerable role in fighting SARS and is an effective treatment. However, several American physicians are skeptical and believe the results of ribavirin have been unsatisfactory. A recent study by the United States Army Medical Research Institute found

no evidence that ribavirin had any effect on SARS-infected tissues.<sup>18</sup>

Severe acute respiratory syndrome researchers have been paying particular attention to a naturally found substance named quercetin due to the fact that quercetin in conjunction with vitamin C has been found to be an effective aminopeptidase inhibitor.<sup>29</sup> Aminopeptidase is an enzyme that causes the breakdown of collagen thereby permitting the cellular invasion of the RNA virus. By inhibiting aminopeptidase, quercetin can reduce the infectivity of a virus.<sup>30</sup> In fact, a study found quercetin to be quite effective in inhibiting coronaviruses.<sup>25</sup>

Possibly the most unique SARS treatment is practiced by a Hong Kong doctor who claims a 60% success rate.<sup>31</sup> The treatment involves a transfusion of blood serum from recovering SARS patients.<sup>31</sup> These patients have built up antibodies to fight the virus. These antibodies can be transferred in the form of the serum to another SARS patient at an earlier stage of the illness. The antibodies in the second patient aid the patient's own immune system in fighting the disease. The results of this treatment have been encouraging. They indicate that the blood serum treatment is more effective than antiviral and steroid treatments. In fact, none of the individuals who have received the blood serum treatment have died and many of them have recovered more quickly than those who have not received the serum.<sup>31</sup>

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