Review Article

Severe Acute Respiratory Syndrome (SARS)

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ABSTRACT

Severe acute respiratory syndrome (SARS) is a serious form of pneumonia. It is caused by a virus that was first identified in 2003. Infection with the SARS virus causes acute respiratory distress (severe breathing difficulty) and sometimes death. SARS is a dramatic example of how quickly world travel can spread a disease. It is also an example of how quickly a connected health system can respond to a new health threat. Investigations had soon ruled out a novel influenza virus strain, possibly of avian origin, as the cause of SARS. members of the Paramyxoviridae family, including human metapneumovirus and Chlamydia-like organisms, including Chlamydia pneumonia. SARS-associated coronavirus has recently been proved to be the cause of SARS. The SARS virus enters the body through the respiratory tract and first infects the epithelial cells of the trachea, bronchi, bronchioles, and lungs. The virus infects resident, infiltrating, and circulating immune cells. The circulating immune cells carry the virus to other organs.The virus infects and damages the immune cells of the spleen, peripheral and central lymph nodes, and other lymphoid tissues. The immune defense is weakened significantly, which leads to rapid deterioration of the pneumonia.

Keywords: SAARS, Coronavirus, Acute Respiratory Distress Syndrome (Severe Breathing Difficulty), Viral Disease.

INTRODUCTION[1,3]

Severe acute respiratory syndrome (SARS)

Severe acute respiratory syndrome (SARS) is a serious form of pneumonia. It is caused by a virus that was first identified in 2003. Infection with the SARS virus causes acute respiratory distress (severe breathing difficulty) and sometimes death. SARS is a dramatic example of how quickly world travel can spread a disease. It is also an example of how quickly a connected health system can respond to a new health threat. World Health Organization (WHO) physician Dr. Carlo Urabanisss identified SARS as a new disease in 2003. He diagnosed it in a 48-year-old businessman who had traveled from the Guangdong province of China, through Hong Kong, to Hanoi, Vietnam. The businessman and the doctor who first diagnosed SARS both died from the illness. In the meantime, SARS was spreading. Quickly it infected thousands of people around the world, including people in Asia, Australia, Europe, Africa, and North and South America. Schools closed throughout Hong Kong and Singapore. National economies were affected.

The WHO identified SARS as a global health threat, and issued a travel advisory. WHO updates closely tracked the spread of SARS. It wasn't clear whether SARS would become a global pandemic . The fast global public health response helped to stem the spread of the virus. By June 2003, the number of new cases was down enough that on June 7, the WHO stopped its daily reports. But even though the number of new cases dwindled and travel advisories began to be lifted, every new case had the potential to spark another outbreak. SARS appears to be here to stay. It has changed the way that the world responds to infectious diseases during a time of widespread international travel. The 2003 outbreak had an estimated 8,000 cases and 750 deaths.

Etiological factor[5]

On 17 March 2003, the WHO set up a worldwide network of virological laboratories investigating SARS cases (World Health Organization, 2003a). The investigations conducted by the members of these networks were coordinated by WHO's Department of Communicable Disease Surveillance and Response (CSR) through normally daily telephone conferences and a password-protected internet website. Thus results and planned further studies were communicated and views and comments exchanged almost in

"real-time" which made possible the rapid progress in elucidating the aetiological agent. In its final form, this network comprised 13 participating laboratories from ten countries (World Health Organization Multicentre Collaborative Network for Severe Acute Respiratory Syndrome Diagnosis, 2003). Investigations had soon ruled out a novel influenza virus strain, possibly of avian origin, as the cause of SARS, and then focussed on members of the Paramyxoviridae family, including human metapneumovirus and Chlamydia-like organisms, including Chlamydia pneumoniae. However, further investigations did not confirm these findings; the said agents were indeed found in a number of SARS patients but not in all multicentre collaborative networks for severe acute respiratory syndrome Almost nobody knew at that stage that virologists in Beijing had already discovered a new virus in samples from some of the earliest SARS patients. However, the official line in China at the time was that the novel enormous scales, and when the disease's ability to spread to distant areas within a very short period of time became obvious (World Health Organization, 2003d). A definition was developed for suspected and probable SARS cases, based on clinical and epidemiological criteria; it has since been modified on several occasions. As of September 2003, 8098 "atypical pneumonia" was caused by Chlamydia Nevertheless, before the end of March, laboratories in Hong Kong, Germany, Canada, and the United States of America found evidence of a novel coronavirus in patients with SARS by cell culture, electron microscopy, and by polymerase chain reaction (PCR) using primers at low stringency designed for other agents followed by sequencing These results could not rule out that very thorough and extensive testing had by chance led to the discovery of a novel agent that was not responsible for the new illness but rather an "innocent bystander". However, the sequences obtained in different parts of the world were shown to belong to the same, previously unrecognised, coronavirus It could also be shown that SARS patients underwent seroconversion against this coronavirus, using cells infected with patient isolates as antigen for indirect immune fluorescent antibody tests Furthermore, no evidence of present or past infection with this agent could be detected in limited surveys of healthy control individuals not suffering from SARS This strengthened the case for the novel coronavirus being the cause of SARS, but only after it had been shown to cause a similar illness in artificially infected macaques could it be regarded as fulfilling all four of Koch's postulates World Health Organisation Multicentre Collaborative Networks for Severe Acute Respiratory Syndrome Diagnosis, 2003). On April 16, 2003, less than a month after the laboratory network had been brought into existence, WHO officially announced that a new coronavirus, never before seen in humans or animals and now provisionally termed SARS associated coronavirus (abbreviated as SARS-CoV), was the cause of SARS and Peiris et al. 1 provides a dramatic example of an emerging coronavirus disease in humans, described by Poutanen 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. The Figure shows the structure of the vireos.

Information regarding to coronavirus[4,5,6]

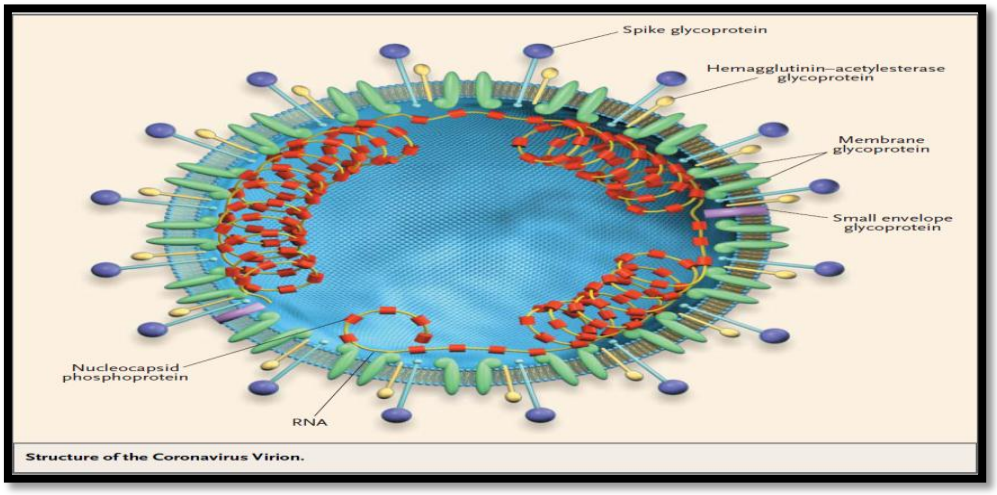

Fig. Structure of the Coronavirus Virion

The disease is usually most severe in neonates. The signs of infection in immune suppressed animals may differ from those in immunocompetent animals; immune suppressed animals may also shed virus for prolonged periods and accumulate and possibly spread mutant viruses. The detection of SARS-associated corona virus in fecal and serum samples from patients, as well as in respiratory specimens, suggests that this virus, like many animal corona viruses, 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 corona virus infections, making certain species or strains of animals highly susceptible to lethal infection. For example, corona viruses from domestic cats almost always cause death in cheetahs. Coinfection with other viruses, parasites, or bacteria exacerbates some animal coronavirus diseases. The deaths 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 acetylesterase 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.

Pathogenesis of SARS[4,5,11]

Based on our findings, we propose the following pathogenesis mechanism of SARS. The SARS virus enters the body through the respiratory tract and first infects the epithelial cells of the trachea, bronchi, bronchioles, and lungs. The virus infects resident, infiltrating, and circulating immune cells. The circulating immune cells carry the virus to other organs. The virus infects and damages the immune cells of the spleen, peripheral and central lymph nodes, and other lymphoid tissues. The immune defense is weakened significantly, which leads to rapid deterioration of the pneumonia. In the same manner, the blood-borne SARS virus infects other organs. As such, patients who have compromised immune function, such as those who have chronic diseases and aged individuals, suffer a more severe illness and have a much higher mortality from SARS .The extent of immune cell damage, reflected by lymphocyte count, is a manifestation of the patient's immune status and a predictor of outcome. The damage to the immune system, more than damage to the lungs, determines whether a patient recovers or dies from the infection. In a way, the name "sudden acute respiratory syndrome" is inappropriate because it diverts attention from the primary pathologic changes that result from SARS virus infection. It must be emphasized that immune damage most likely is the primary determinant of clinical outcome. This study unveils a hitherto unknown, but significant, aspect of the pathogenesis of SARS. Our proposed mechanism of infection and dissemination is capable of explaining all of the clinical symptoms and laboratory findings that have been reported for SARS. It provides a comprehensive theory of pathogenesis for this new disease. In a way, SARS infection is similar to HIV infection that causes AIDS. Although HIV attacks and destroys the target cells slowly, particularly lymphocytes (24), SARS virus infects and destroys the immune cells in a much faster and more devastating fashion. Like many other infectious diseases, SARS infections show differing degrees of severity in different individuals. Only the most severe cases demonstrate the full range of pathologic changes that was described above. Our findings suggest that body fluid and fecal–respiratory tract transmission of the virus, although not reported, is possible because SARS viruses or its sequences are detectable in the blood, intestines, stool, and urine. A

correct understanding of the pathogenesis is crucial for developing animal models to test effective vaccines and to establish techniques for early diagnosis. Further detailed studies of the immune damage will shed more light on the true nature of the pathogenesis of SARS.

Clinical feature[11,12]

SARS has affected persons in all age groups; there has been a slight predominance of female patients, which is probably related to the increased likelihood of exposure among nurses. 22 SARS has also been reported in immune compromised patientsand pregnant women, but the numbers of reported cases are too small to permit any judgment as to whether the outcome was more or less severe in such patients. Infected persons present initially with fever, myalgia, malaise, and chills or rigor (Cough is common, but shortness of breath, tachypnea, or pleurisy is prominent only later in the course of the illness. Unlike other atypical pneumonias caused by mycoplasma or chlamydia, SARS is less= commonly manifested as upper respiratory symptoms such as rhinorrhea and sore throat. A watery diarrhea occurs in some patients later in the course of the illness (Table 2). Respiratory signs such as rales are present in less than one third of cases, and their severity often seems lower than would be expected on the basis of the findings on radiography of the chest. 5 Afebrile casesof SARS can occur in the elderly, who may present with malaise and decreased appetite. In such patients, the presenting problem may even be a fall and fracture. Lymphocytopenia is common, and in some patients the platelet count is depressed, with concomitant increases in the level of d-dimers and the activated partial-thromboplastin time. However, these laboratory findings do not allow reliable discrimination between SARS and other causes of community acquired pneumonia. Depending on the interval between the onset of fever and hospital admission, the initial chest radiograph is abnormal in 60 to 100percent of cases A high-resolution computed tomographic (CT) scan is abnormal in 67 percent of patients with initially normal chest radiographs. The most common initial radiographic abnormalities are ground-glass opacifications that do not obscure the view of underlying vessels or focal consolidations of the peripheral, subpleural, and lower zones of the lungs Mediastinal lymphadenopathy, cavitation, and pleural effusions are rare. One third of patients with SARS have improvement, with defervescence and resolution of radiographic changes. The other two thirds have persistent fever, increasing shortness of breath, tachypnea, oxygen desaturation, worsening of chest signs on physical examination, and the onset of diarrhea. Serial chest radiographs or CT scans reveal the progression of the original abnormality into unilateral or bilateral multifocal air-space consolidations. Shifting or fluctuating radiographic shadows have been noted. Pneumomediastinum without preceding positive pressure ventilation or intubation is a characteristic radiographic sign of SARS. The subpleural pneumonic process may cause a pleurodesis-like effect, and the diffuse alveolar damage has led to fibrosis and the formation of cysts. The air leak resulting from the rupture of these cysts can only dissect along the bronchovascular bundle, thereby causing pneumomediastinum, an unusual complication. About 20 to 30 percent of patients require admission to an intensive care unit, and most of them require mechanical ventilation A low-tidal-volume strategy for the protection of the lungs has usually been used for ventilation, with volume-control or pressure-control ventilation targeting tidal volumes of 6 ml per kilogram of predicted body weight and plateau pressures of less= than 30 cm of water. 64 Positive end-expiratory pressure, the fraction of inspired oxygen, and the ventilator rates have then been adjusted to maintain a partial pressure of arterial oxygen of more than 55 mm Hg (oxygen saturation as measured by pulse oximetry, >88 to 90 percent), with or without permissive hyper capnia. The terminal event has been severe respiratory failure, multiple organ failure, sepsis, or inter current medical illness such as acute myocardial infarction. Residual ground-glass opacifications have been noted on follow-up chest radiographs and CT scans obtained about one month after admission in 80 percent and 95 percent of patients, respectively, who recovered from SARS. CT scans have shown signs of fibrosis (including traction bronchiectasis and parenchymal bands) and peribronchovascular interstitial thickening. 58 Between 6 and 20 percent of discharged patients have had some degree of respiratory impairment that might be related to residual lung fibrosis, muscle weakness, and systemic effects of the viral illness. Post-traumatic stress disorder and depression are common among patients with SARS and persist beyond the period of hospitalization. 66 Further follow-up isrequired for the detection of other long-term complications of corticosteroid treatment, such asavascular necrosis of bone. Pathological analysis of the lung at autopsy in patients who died within 10 days after the

onset of illness revealed diffuse alveolar damage, desquamation of pneumocytes, an inflammatory infiltrate, edema, and hyaline-membrane formation. In patients who died later in the course of illness, organizing diffuse alveolar damage was seen, with squamous metaplasia and multinucleate giant cells of either macrophage or epithelial-cell origin.

Symptoms[1,3,9]

The hallmark symptoms are

- Cough
- Difficulty breathing
- Fever greater than 100.4 degrees F (38.0 degrees C)
- Other breathing symptoms

The most common symptoms are

- Chills and shaking
- Cough -- usually starts 2-3 days after other symptoms
- Fever
- Headache
- Muscle aches

Less common symptoms include

- Cough that produces phlegm (sputum)
- Diarrhea
- Dizziness
- Nausea and vomiting
- Runny nose
- Sore throat

In some people, the lung symptoms get worse during the second week of illness, even after the fever has stopped.

Table 2. Initial Clinical Presentation of Adults with SARS.*

Variable	China	Hong Kong	Canada	Singapore	All Four Countries
Demographics					
No. of cases reported	190	388	154	20	752
Age of patients — yr	Range, 16–84	Mean, 42.9	Median, 45	Median, 28	NA
Sex					
Male — no.	70	174	94	5	343
Female — no.	120	214	60	15	409
Ratio of male to female	0.58:1	0.8:1	1.57:1	0.33:1	0.84:1
Clinical features — no./total no. (%)					
Fever	190/190 (100.0)	388/388 (100.0)	153/154 (99.4)	20/20 (100.0)	751/752 (99.9)
Chill or rigors	89/190 (46.8)	245/378 (64.8)	40/144 (27.8)	3/20 (15.0)	377/732 (51.5)
Myalgia	114/190 (60.0)	169/388 (43.6)	73/154 (47.4)	9/20 (45.0)	365/752 (48.5)
Malaise	179/190 (94.2)	72/175 (41.1)	57/154 (37.0)	9/20 (45.0)	317/539 (58.8)
Rhinorrhoea	NM	44/198 (22.2)	3/144 (2.1)	3/20 (15.0)	50/362 (13.8)
Sore throat	NM	65/378 (17.2)	21/154 (13.6)	5/20 (25.0)	91/552 (16.5)
Cough	175/190 (92.1)	162/338 (47.9)	108/154 (70.1)	15/20 (75.0)	460/702 (65.5)
Dyspnea	175/190 (92.1)	31/250 (12.4)	68/154 (44.2)	8/20 (40.0)	282/614 (45.9)
Chest pain or pleurisy	41/190 (21.6)	3/10 (30.0)	3/10 (30.0)	NM	47/210 (22.4)
Anorexia	NM	37/188 (19.7)	NM	NM	37/188 (19.7)
Nausea or vomiting	NM	NM	1/10 (10.0)	7/20 (35.0)	8/30 (26.7)
Diarrhea	46/190 (24.2)	45/303 (14.9)	39/154 (25.3)	NM	130/647 (20.1)
Headache	116/190 (61.1)	118/388 (30.4)	54/154 (35.1)	4/20 (20.0)	292/752 (38.8)
Dizziness	89/190 (46.8)	68/263 (25.9)	6/144 (4.2)	NM	163/597 (27.3)
Physical signs — no./total no. (%)					
Tachycardia	NM	NM	71/154 (46.1)	NM	71/154 (46.1)
Tachypnea	NM	NM	60/154 (39.0)	NM	60/154 (39.0)
Chest rales	NM	19/50 (38.0)	37/154 (24.0)	NM	56/204 (27.5)

* SARS denotes severe acute respiratory syndrome, NA not applicable, and NM not mentioned (in the relevant reports).

Diagnosis[11,24]

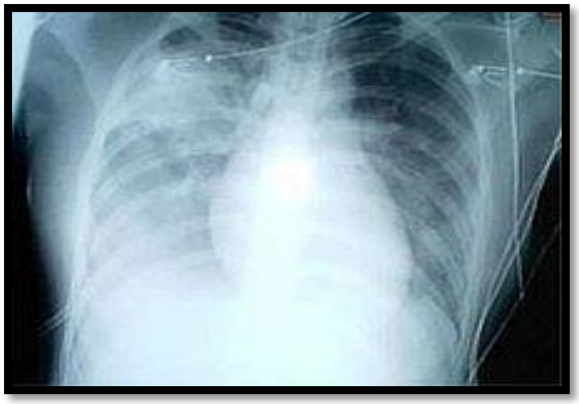

Fig. A chest X-ray showing increased opacity in both lungs, indicative of in a patient with SARS

SARS may be suspected in a patient who has

1. Any of the symptoms, including a fever of 38 °C (100.4 °F) or higher, and
2. Either a history of:

- Contact (sexual or casual, including tattoos) with someone with a diagnosis of SARS within the last 10 days OR
- Travel to any of the regions identified by the WHO as areas with recent local transmission of SARS (affected regions as of 10 May 2003 were parts of China, Hong Kong, Singapore and the province of Ontario, Canada). A probable case of SARS has the above findings plus positive chest X-ray findings of atypical pneumonia or respiratory distress syndrome.With the advent of diagnostic tests for the coronavirus probably responsible for SARS, the WHO has added the category of "laboratory confirmed SARS" for patients who would otherwise fit the above "probable" category who do not (yet) have the chest X-ray changes, but do have positive laboratory diagnosis of SARS based on one of the approved tests (ELISA, immune fluorescence or PCR). The chest X-ray (CXR) appearance of SARS is variable. There is no pathognomonic appearance of SARS, but is commonly felt to be abnormal with patchy infiltrates in any part of the lungs. The initial CXR may be clear. White blood cell and platelet counts are often low. Early reports indicated a tendency to relative neutrophilia and a relative lymphopenias — relative because the total number of white blood cells tends to be low. Other laboratory tests suggest raised lactate dehydrogenase and slightly raised creatine kinase and C-reactive protein levels. With the identification and sequencing of the RNA of the coronavirus responsible for SARS on 12 April 2003, several diagnostic test kits have been produced and are now being tested for their suitability for use. Three possible diagnostic tests have emerged, each with drawbacks. The first, an enzyme-linked immunosorbent assay (ELISA) test detects antibodies to SARS reliably, but only 21 days after the onset of symptoms. The second, an immuno fluorescence assay, can detect antibodies 10 days after the onset of the disease, but is a labour- and time-intensive test, requiring an immune fluorescence microscope and an experienced operator. The last test is a polymerase chain reaction (PCR) test that can detect genetic material of the SARS virus in specimens from blood, sputum, tissue samples and stools. The PCR tests so far have proven to be very specific, but not very sensitive.

Management[22,25,31]

Severe acute respiratory syndrome (SARS) has recently been recognised as a newly emerging infectious disease that is highly contagious with significant morbidity and mortality. The first index case in Hong Kong was admitted on Feb 22, 2003. As of April 6, 842 cases have been identified in Hong Kong, with fatal complications in 22 patients. The outbreak has prompted the Hospital Authority of Hong Kong and the Department of Health to implement a series of public health measures and hospital policies for the diagnosis and management of patients with SARS. The figures are summaries of the management flowchart in the accident and emergency department for patients with a history of definite contact with SARS patients within the past 10 days and for patients with no such definite contact .The Hong Kong Hospital Authority SARS Command Centre has been established to coordinate clinical activities, including identification and reporting of cases, implementation of infection-control measures, dissemination of information to the public, development of diagnostic tests, and assessment of treatment regimens in a cluster network of hospitals.

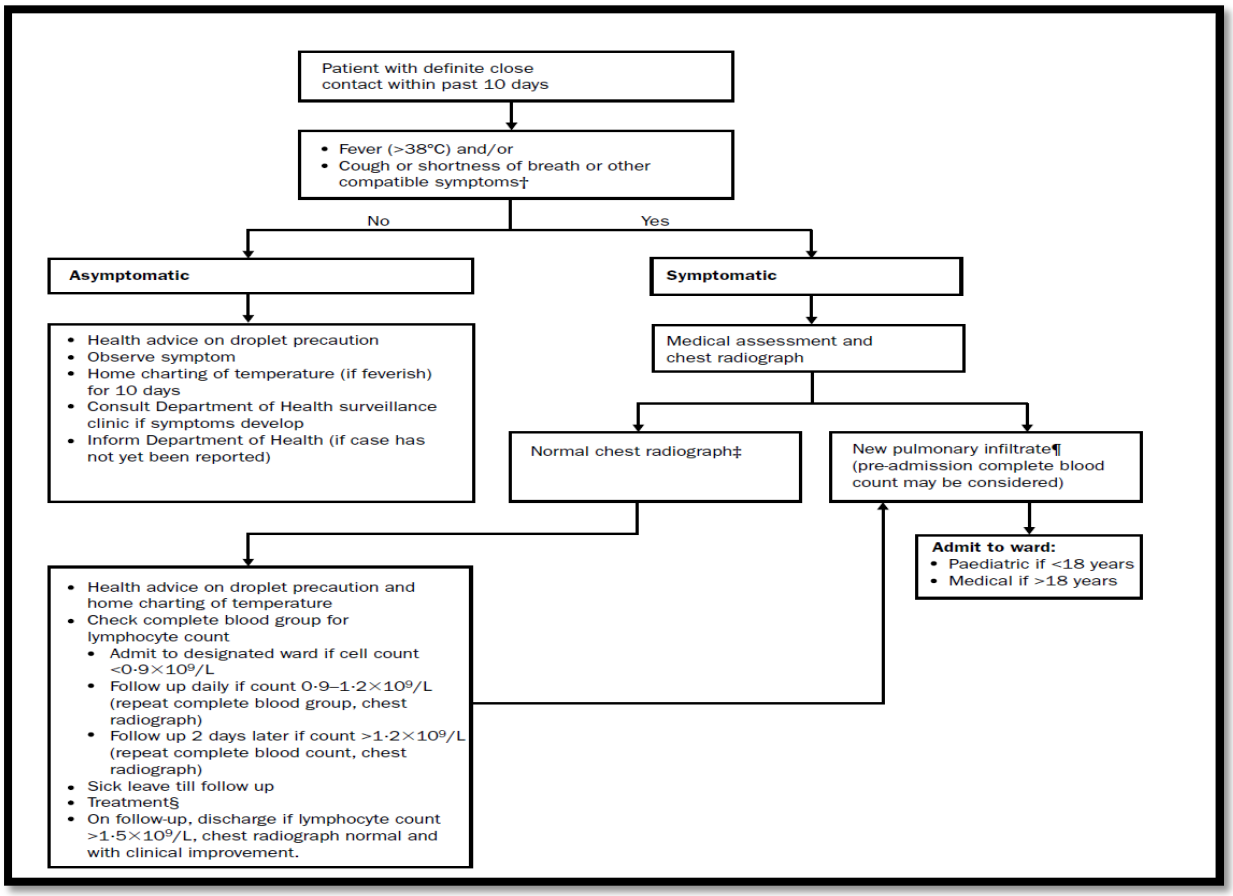

Figure 1: Accident and emergency department management for person with definite contact* with person with severe acute respiratory syndrome (SARS) within past 10 days

Treatment[6,9,19]

Antibiotics are ineffective, as SARS is a viral disease. Treatment of SARS so far has been largely supportive with antipyretics, supplemental oxygen and ventilation support as needed. Suspected cases of SARS must be isolated, preferably in negative pressure rooms, with complete barrier nursing precautions taken for any necessary contact with these patients. There was initially anecdotal support for steroids and the antiviral drug ribavirin, but no published evidence has supported this therapy. Researchers are currently testing all known antiviral treatments for other diseases, including AIDS, hepatitis, influenza and others of the SARS-causing coronavirus. Some of the more serious damage in SARS may be due to the body's own immune system overreacting to the virus – a cytokine storm. Research is continuing in this area. In December 2004, Chinese researchers were reported to have produced a SARS vaccine; it has been tested on a group of 36 volunteers, 24 of whom developed antibodies against the virus. A 2006 systematic review of all the studies done on the 2003 SARS epidemic found no evidence that antivirals, steroids or other therapies helped patients. A few suggested they caused harm.[18] The clinical treatment of SARS has been relatively ineffective, with most high risk patients requiring artificial ventilation. Currently, corticosteroids and ribavirin are the most common drugs used for treatment of SARS In vitro studies of ribavirin have yielded little results at clinical, nontoxic concentrations. Better combinations of drugs that have yielded a more positive clinical outcome (when administered early) have included the use of Kaletras, ribavirins and corticosteroids. The administration of corticosteroids, marketed as Prednisone, during viral infections has been controversial. Lymphopenia can also be a side effect of corticosteroids, even further decreasing the immune response and allowing a spike in the viral load, yet physicians must balance the need for the anti-inflammatory treatment of corticosteroids Clinicians have also noticed positive results during the use of human interferon and glycyrrhizin. No compounds have yielded inhibitory results of any significance. The HIV protease inhibitors ritonavir and saquinavir did not show any inhibitory effect at nontoxic levels. Imino

cyclitol 7 has been found to have an inhibitory effect on SARS-CoV in that it disrupts the envelope glycoprotein processing. Iminocyclitol 7 specifically inhibits the production of human fucosidase and in vitro trials yielded promising results in the treatment of SARS, yet one problem exists

Conclusions[1,3,22,]

Like many of the other 30 or so new pathogens that have been recognized in the past three decades, SARS-CoV may have originated in animals. However, unlike most of these other pathogens, it has become efficient at human-to-human transmission, and this development accounts for the global scale of the disease. In this respect, SARS-CoV resembles the human immunodeficiency virus. The SARS outbreak also serves to illustrate the potential health effects of more transmissible diseases, such as pandemic influenza, and highlights the need for preparedness to meet such threats. It is difficult to make predictions regarding the resurgence of SARS, but the current information suggests that the greatest risk of the reemergence of the disease may derive from an animal reservoir or infections transmitted in the laboratory.20,32 Appropriate containment measures in diagnostic and research laboratories must therefore be strengthened. Given the fact that SARS-CoV has been isolated

from some animals used for food, decisions about reintroducing such animal species into exoticfood markets must be based on a proper assessment of the risks involved. SARS-CoV may also survive between seasons, owing to unrecognized ongoing disease transmission in humans in some parts of the world — for example, asymptomatic carriers or immunocompromised patients. However, current data suggest that these are less likely to be a source of the reemergence of SARS. Active surveillance for clusters of cases of severe respiratory disease must be a priority, especially among health care workers. Such surveillance should include the rapid diagnosis and prevention of other respiratory viruses that cause outbreaks of febrile respiratory disease — notably, influenza. Surveillance and astuteness on the part of clinicians are the keys to the early detection of any reemergence before it regains a foothold in the community.

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