Turk J Med Sci
33 (2003) 265-270

PERSPECTIVES IN MEDICAL SCIENCES

Severe Acute Respiratory Syndrome (SARS): The First Pandemic of the New Century

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Received: July 10, 2003

Severe acute respiratory syndrome (SARS) is an acute respiratory illness caused by a newly described coronavirus (1-3). The epidemic started in early November 2002 in Guandong province, China; however it remained unreported until mid-February 2003 (4). During this period, the disease rapidly spread to other countries. The Hong Kong Special Administrative Region of China and Vietnam were the other 2 countries reporting cases by mid-March, before Singapore and Canada joined the list (5-8). The disease presents a non-specific respiratory illness characterized by high fever, chills, headache and muscle ache. Radiological findings are compatible with atypical pneumonia. The disease, may then progress to acute respiratory distress syndrome (ARDS), which is the main cause of mortality among patients (5,7). The causative virus is predominantly spread by droplets or by direct and indirect contact (9). Viral shedding in feces and urine has also been described. Health care workers in hospitals are among those commonly infected (5). The following review intends to provide a comprehensive background on the several aspects of this newly described disease.

Epidemiology and timeline of the pandemic

SARS established its special place in the history of infectious diseases for which an etiological agent was detected in record time while the genetic sequencing of the virus was materialized shortly thereafter. The characteristics of epidemics in the most –hard-hit countries and elsewhere were described by collaborative team work provided by scientists in different countries. It was this cooperation that helped halt the epidemic. This collaborative work also resulted in the release a batch of diagnostic tests; however, no commercial tests had hit the market at the time of writing. Similarly, no spesific treatment modality has been made available so far, hence patients receive supportive therapy and/or are treated with antivirals with no proven activity against the etiological agent.

Although the initial cases of SARS were traced back to mid-November 2002, the first report about the disease was released by the World Health Organization (WHO) on 14 February, 2003, indicating that 305 cases and 5 deaths from an influenza-like illness had occurred between 16 November 2002 and 9 February 2003 in Guangdong province, China. (4). At the end of February, Hong Kong and Vietnam reported outbreaks of a severe form of pneumonia. Among those who succumbed to the disease was Dr. Carlo Urbani, a WHO epidemiologist who reported the first data of the epidemic in Vietnam on 28 February. WHO called the new syndrome as “severe acute respiratory syndrome”, i.e. SARS, on 10 March (10).

A global alert was issued on 12 March by WHO about the mysterious pneumonia, which included a travel alert for the affected areas. By then, cases had also identified in Singapore and Canada (7,8).

At the end of March, the number of suspected and/or probable cases (see below for case definitions) exceeded 1300, 49 of whom died, and the disease had spread to 8 countries. The local transmission of SARS was confirmed in Canada, Hong Kong, Singapore, Taiwan and Vietnam. The Centers for Disease Control and Prevention (CDC) of the United States reported a cluster of 12 patients with

the disease in Hong Kong whose infection could be traced back to a doctor from southern China who arrived on 21 February 2003 and stayed in a local hotel. A continued steep rise in the number of SARS cases was detected in a large housing estate (Amoy Gardens) consisting of ten 35-storey blocks, which are home to around 15,000 persons. A detailed epidemiological investigation found that a single patient with diarrhea who transmitted the disease to 321 residents was the source of the outbreak. A detective–like epidemiological investigation revealed that the rapid spread of SARS in this case involved defective U-traps in bathrooms, an amplifying effect of bathroom exhaust fans, a cracked sewer vent pipe, and an aerodynamic effect in a lightwell which bathroom windows opened onto (11). The residents were isolated for 10 days in their flats and were subsequently moved to rural isolation camps for 10 days.

As of 1 July, the number of probable cases reported by WHO was 8445 from 33 different countries or regions of the world (12). The highest figures came from China from where a total of 5327 cases with 348 deaths were reported. Hong Kong was the second with 1755 cases and 298 deaths, and Taiwan reported 678 probable cases and 84 deaths. Singapore, one of the hardest-hit countries in the early stages of the epidemic, recorded 206 cases and 32 deaths. On 28 April, Vietnam became the first country to stop local transmission of SARS. Thereafter, strict screening and preventive measures imposed by WHO and local health authorities in affected countries led to the infection being controlled from the second half of May. Currently WHO does not advise the imposition of restrictions for travellers to any area of the world, passengers screening from Toronto and Taiwan is recommended (13).

Case definitions

The WHO case definitions for surveillance purposes were revised on 1 May 2003 and are summarized below (14). The final version of these definitions includes laboratory test results that will be explained further in the text. Since none of the diagnostic tests have been proved to be accurate, SARS remains a diagnosis of exclusion.

Suspect case

1) A person presenting after 1 November 2002 with a history of:

   high fever (>38 °C) and cough or breathing difficulty and one or more of the following exposures during the 10 days prior to onset of symptoms:

   close contact with a person who is a suspected or probable case of SARS

   history of travel to an area with recent local transmission of SARS, or

   residing in an area with recent local transmission of SARS

2) A person with an unexplained acute respiratory illness resulting in death after 1 November 2002, but on whom no autopsy has been performed, and one or more of the following exposures during the 10 days prior to onset of symptoms:

   close contact with a person who is a suspected or probable case of SARS,

   history of travel to an area with recent local transmission of SARS, or

   residing in an area with recent local transmission of SARS.

Close contact defines a person who cared for, lived with, or had direct contact with

respiratory secretions or body fluids of a suspected or probable case of SARS.

Probable case

1) A suspected case with radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest X-ray.

2) A suspected case of SARS that is positive for SARS coronavirus by one or more assays.

3) A suspected case with autopsy findings consistent with the pathology of RDS without an identifiable cause.

A case should be excluded if an alternative diagnosis can fully explain the illness.

The etiological agent (SARS-associated coronovirus "SARSCoV")

A network of 11 laboratories in 9 countries was established by WHO on March 17 for multicenter research on the etiology of SARS and to simultaneously develop a diagnostic test. Within 2 weeks a novel coronavirus was isolated by laboratories in Hong Kong, Germany and the United States (1-3). The new virus was designated SARS-associated coronavirus (SARSCoV). It had never been seen in humans or animals, and had only a moderate relationship with other previously known human coronaviruses. Shortly thereafter, complete

genome sequences of the new coronavirus (15-16) were published by a Canadian laboratory and the CDC. The sequence analysis provided further evidence that SARSCoV is an animal virus that has been able to cross the species barrier (10). Actually, there has been some speculation from Hong Kong indicating that SARSCoV may have jumped to humans from wild animals like civet cats, which are considered a delicacy in southern China (17).

The coronaviruses are members of a family of large, enveloped, positive-stranded RNA viruses and are associated with a variety of diseases including mild gastroenteritis and mild respiratory tract infections in humans and domestic animals. SARSCoV is the first coronavirus to cause severe disease in humans (15,16,18).

While the known human coronaviruses are able to survive on environmental surfaces for up to 3 h, the initial evidence indicates that SARSCoV survives in feces and urine at room temperature for at least 1-2 days. The stability is up to 4 days in stools from patients with diarrhea (the pH of which is higher than that of a normal stool). The virus can survive in cell cultures after 21 days at 4 °C and 80 °C. After 48 h at room temperature, on several surfaces including plastic ones, the concentration of the virus is reduced by one log only, indicating that the virus is more stable than other known human coronaviruses under these conditions. Heating to 56 °C and exposure to different commonly used disinfectants and fixatives including household bleach and 75% alcohol inactivate SARS-CoV within 5 minutes (19).

Symtoms and clinical findings:

SARS is usually presented with nonspecific clinical findings resembling those of atypical pneumonia. The incubation period varies between 2-10 days after which patients develop fever (>38.0 °C), chills, rigors, headache, dizziness, malaise and myalgia. Although sputum production, sore throat, coryza, nausea and vomiting, and diarrhea are reported to be less common (6,8), in some clusters of patients the incidence of these symptoms differed considerably. For instance, the incidence of diarrhea in patients from Amoy Gardens in Hong Kong was around 50%, whereas it was only 2-4% in others (11). Physical examination was unrevealing, excluding high body temperature that was observed in most patients, while inspiratory crackles could be heard at the base of the lungs in some (10).

The severity of the illness ranges from mild to moderate symptoms to a severe disease process with respiratory failure due to ARDS and death. Clinical deterioration requiring intensive care and ventilatory support generally occurs 7 to 10 days after the onset of symptoms (3,6). The case fatality ratio of SARS ranges from 0% to 50% depending on the age group affected: less than 1% in persons aged 24 years or younger; 6% in persons aged 25 to 44 years; 15% in persons aged 45 to 64 years; and greater than 50% in persons aged 65 years and older (10).

SARS has been reported to cause a milder clinical course in younger children in comparison to that seen in adults and teenagers (20). Only a minority of the patient population (3%) in Hong Kong was made up of children less than 15 years of age, and they accounted for only 3 % of all cases. So far, no explanation has been provided for this. The symptoms in teenage patients were similar to those seen in adults, whereas the younger children (<12 years) presented mainly with a cough and runny nose, and none had chills, rigor or myalgia. In addition, the radiological changes were milder and generally resolved more quickly than in the teenagers.

Laboratory and radiological findings

The most common laboratory abnormalities include lymphopenia, leukopenia, thrombocytopenia, elevated lactate dehydrogenase levels, elevated aspartate aminotransferase levels and elevated creatine kinase levels of non-cardiac origin (6,7,10,21).

Chest X-ray may be normal during incubation period and throughout the course of the illness. However, air-space consolidation represented by unilateral patchy infiltrates which progress to bilateral multilobar infiltration are commonly seen in most patients. In clinically deteriorating patients these infiltrates become enlarged. CT scan findings are compatible with those of plain radiographs and include areas of subpleural focal consolidation with air bronchograms and groundglass opacities. Radiographically, SARS may be indistinguishable from other severe forms of pneumonia (10).

Laboratory tools for diagnosis

Although several tests have been developed for the diagnosis of SARS, the results of field testing to determine their actual sensitivity and specificity are not available yet. Therefore, the diagnosis of SARS is currently based on clinical and epidemiological findings. Three different types of laboratory tests have been developed (10):

1) Antibody detection

ELISA (Enzyme Linked ImmunoSorbant Assay) detects a mixture of IgM and IgG antibodies in the serum of SARS patients and reliably yields positive results at around day 21 after the onset of illness.

Immunofluorescence assay (IFA) gives earlier positive results around 10 days after the start of symptoms. It requires SARSCoV-infected cells fixed on a microscope slide; patient antibodies bind to viral antigens and are in turn detected by immunofluorescence-labeled secondary antibodies against human IgG or IgM or both, using an immunofluorescence microscope.

2) Molecular tests

The SARSCoV-specific RNA can be detected in various clinical specimens such as blood, stools, respiratory secretions or body tissues by polymerase chain reaction (PCR). Primers have been made publicly available by WHO network laboratories (22). Existing PCR tests are very specific but lack sensitivity. That means that negative tests can not rule out the presence of the SARS virus in patients.

3) Cell culture

Specimens containing the virus, such as from respiratory secretions, blood and stools from SARS patients can also be detected by infecting cell cultures and growing the virus. Once isolated, the virus must be identified as the SARS virus with further tests. Cell culture is a very demanding test, but it is the only means to show the existence of a live virus. Negative cell culture results do not exclude SARS.

Pathological findings

Post mortem histopathological evaluations of lung tissue from patients who died from SARS showed diffuse alveolar damage at various levels of progression and severity, consistent with the pathologic manifestations of ARDS (5,7,11). Among the findings revealed from 6 autopsy cases were bronchial epithelial denudation, loss of cilia and squamous metaplasia. Secondary bacterial pneumonia was present in 1 case. A giant-cell infiltrate was seen in 4 patients, with a pronounced increase in macrophages in the alveoli and the interstitium of the lung. Hemophagocytosis was present in 2 patients. (23)

Routes of transmission

Epidemiological data suggest that the virus is predominantly spread by droplets or by direct and indirect contact (9,24-26). Most of the cases occurred following close contact with patients, including household members and health-care workers, by those who were not protected by contact or respiratory precautions. The infectious virus is present at very high concentrations in the respiratory tract of patients (2). Low amounts of viral RNA have also been detected in the stools of patients late in their convalescence period, making feces a potential route of transmission (2). The airborne spread of SARS does not seem to be a major transmission route. However, the apparent ease of transmission in some instances, such as in Amoy Gardens (see above), is of concern.

Prevention

As mentioned earlier, strict infection control measures have been of utmost importance in order to control the epidemic. Health-care workers, household members of the patients and other people in close contact have been at high risk of contracting the disease. Therefore, detailed preventive measures were described for each of those categories (24). Droplet infection with SARS is the primary route of spread for the virus (9) in the healthcare setting. Surgical and N95 masks provided the best protection for exposed healthcare workers, whereas paper masks did not significantly reduce the risk of infection (9). Since SARSCoV is viable in enviromental surfaces for several days, rigorous disinfection and hygiene procedures are essential for effective protection.

CDC recommended careful hand hygiene for all contact with suspected SARS patients including hand washing with soap and water. If hands are not visibly soiled, alcohol-based handrubs may be used as an alternative to hand washing. For admitted patients, healthcare personnel should exercise contact precautions (e.g., use of gown and gloves for contact with the patient or their environment), and they should wear eye protection for all patient contact. Airborne precautions

should be implemented (e.g., an isolation room with negative pressure relative to the surrounding area and use of an N-95 filtering disposable respirator for persons entering the room). If these precautions cannot be fully implemented, patients should be placed in a private room, and all persons entering the room should wear N-95 respirators (10).

If SARS is suspected in a patient in an outpatient setting a surgical mask should be placed over the patient's nose and mouth. If masking the patient is not feasible, the patient should be asked to cover his/her mouth with a disposable tissue when coughing, talking or sneezing. The patient should immediately be separated from others and isolated in a private room if possible. Those patients who reside at home should wear a surgical mask. If the patient is unable to wear a surgical mask, household members should wear surgical masks when in close contact with the patient (10).

Treatment

No effective treatment regimen has been described (27). For patients with progressive deterioration, intensive and supportive care is of primary importance. During the peak of the epidemic the patients were treated most frequently with ribavirin and steroids, although the efficacy of these drugs has not been proven in the absence of clinical indicators. Ribavirin is recommended to be given 8 mg/kg every 8 h intravenously or 1.2 g every 12 h orally, with an oral loading dose of 4 g for those with normal renal function tests. Recommended duration of therapy is for 7-14 days. Hydrocortisone 2 mg/kg is given every 6 h or 4 mg/kg every 8 h intravenously. Dose reduction and stopping the drug course over 1 week is recommended when there is clear clinical improvement. For severe and rapidly deteriorating cases methylprednisolone 10 mg/kg every 24 h intravenously for 2 days is given, and then the therapy is continued with hydrocortisone as above (5,8,10,28,29). Usually patients received antibacterial agents such as macrolides or respiratory quinolones (e.g. levofloxacin) for typical and atypical microorganisms for 7-14 days.

Voluntary home isolation is recommended for those in contact with probable SARS cases and each contact should be visited or telephoned daily by a member of a public health care team. If the contact develops disease symptoms, the contact should be investigated locally at an appropriate health care facility. The most consistent first symptom that is likely to appear is fever.

Future aspects of the disease

WHO reported on 18 June that SARS was being brought under control (27), but warned that many unanswered questions still existed including the reservoir(s) of the virus, possible seasonal recurrence and the contribution of environmental contamination to transmission. Therefore, the need for at least a full year of surveillance is proposed to determine whether the disease has established endemicity and to ensure that no cases have spread, but remained undetected, to countries with poor surveillance and reporting systems (30). WHO also warned that a high level of vigilance should be maintained for new cases, since the possibility exists that SARSCoV hides somewhere in nature, waiting to find the suitable conditions for the efficient spread of its infection to human hosts.

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