Q J Med 2003; **96**:845–852
doi:10.1093/qjmed/hcg146

Commentary

QJM

Severe acute respiratory syndrome: global initiatives for disease diagnosis

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Summary

We present a retrospective analysis of the available articles on severe acute respiratory syndrome (SARS) published since the outbreak of the disease. SARS is a new infectious disease caused by a novel coronavirus. Originating in Guangdong, Southern China, at the end of 2002, it has spread to regions all over the world, affecting more than 8000 people. With high morbidity and mortality, SARS is an important respiratory disease which may be encountered world-wide. The causative virus was identified by a WHO-led network of laboratories, which identified the genome sequence and developed the first molecular assays for diagnosis. For the respiratory physician, detecting SARS in its earliest stages, identifying pathways of transmission, and implementing preventive and therapeutic strategies are all important. The WHO and the CDC have published helpful definitions of 'suspected' and 'probable' cases. However, the symptoms of the disease may change, and laboratory tests and definitions are still limited. Even in a situation of no new cases of infection, SARS remains a major respiratory health hazard. As with influenza virus outbreaks, new epidemics may arise at the end of each year.

Introduction

Severe acute respiratory syndrome (SARS) is a new infectious disease with a high morbidity and mortality. It appears to have originated in the province of Guangdong, Southern China, at the end of 2002, and has since affected more than 8000 people, killing more than 800, in a period of 6 months. The disease is caused by a novel coronavirus,[1–3] which has been identified due to the efforts made in a unique global network initiated by the World Health Organization (WHO).

After reports from the Department of Health of Hong Kong about the outbreak of a pneumonia epidemic in Hong Kong public hospitals, and further reports, the WHO issued a first global alert on this atypical pneumonia, also called severe acute respiratory syndrome (SARS) on 12 March 2003. In this period, the WHO also received reports of the syndrome from China and other Asian countries, including Thailand, Indonesia, Singapore, the Philippines, Taiwan, and Vietnam. Similar respiratory

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syndromes were also reported in countries from other continents including North America (Canada, USA) and Europe (Germany).

The first report on the syndrome was made from a hospital in Hanoi by the WHO scientist Carlo Urbani, who died in the epidemic.[4] On 17 March 2003, five days after the initial global alert, the WHO initiated a collaborative multi-center research project on SARS diagnosis by 11 major laboratories in nine countries.[5] This scientific network, used modern communication technologies to optimize the examination of SARS samples, and it was soon shown that the causative agent was a novel coronavirus (SARS-CoV).[1–3] It was proposed that the first isolate of the virus should be named the Urbani strain of SARS-associated coronavirus, in memory of Carlos Urbani.[6]

Parallel to the progress made in the epidemiology and molecular pathophysiology of SARS, clinicians from Hong Kong, China and other countries reported their experience of treating SARS. It is crucial that SARS is detected in its earliest stages and that therapeutic options are optimized. As the symptoms of the disease may change and laboratory tests and definitions are still limited, SARS remains a major health problem even in a situation of decreasing numbers of infections.

We analyse the currently available reports on disease diagnosis and summarize the global initiatives for SARS diagnosis.

Epidemiology

Prior to defining the disease entity and proposing therapeutic options, detailed knowledge of epidemiological data is required. The early cases of SARS most likely occurred in the Guangdong Province in Southern China in November 2002, when many cases of severe pneumonia of unknown aetiology were reported.[7] These cases already had a high rate of transmission to health-care workers.

The first well-documented epidemic spread of SARS took place in Hong Kong.[8,9] A SARS-CoV-infected 64-year-old physician from Southern China, who had symptoms of a respiratory tract infection almost one week before arriving, checked into a hotel on 21 February 2003. The physician died 10 days later of severe pneumonia and in the hotel, the infection spread to eight people who had been hotel guests or who had visited people at the hotel. These eight key people then carried the virus to other countries, with outbreaks in Vietnam,[10] Singapore[11–13] and Canada.[14–16]

In Hong Kong, a 26-year-old man who had been at the hotel for a visit developed symptoms of a febrile illness. He was admitted to the Prince of Wales Hospital on 4 March 2003 and was initially found to have a right upper lobe pneumonia that progressed to bilateral localization. He was treated with nebulized salbutamol and intravenous antibiotics, as a bacterial cause of the pneumonia was presumed. The patient recovered without antiviral or steroidal treatment, but 6 days after his admission, 18 healthcare workers from the same ward also reported signs of an acute febrile illness.[17]

Further investigations revealed a total of 156 subjects with a similar clinical picture who were infected and admitted to hospital between 11 and 25 March. These included 69 healthcare workers and 16 medical students who had been at the index ward. The infected individuals had also visited the index ward.

The infection of a 33-year-old male patient with chronic renal disease undergoing haemodialysis led to a major community outbreak in Hong Kong. This patient was also admitted to the index ward at the Prince of Wales Hospital in the same time period. With the initial main symptom of diarrhoea, the patient visited relatives at an apartment complex, and more than 300 residents were infected, with leaky sewage pipes being the most likely route of virus spread. As the floor drains of the bathrooms and kitchens were connected to the sewage pipes, backflow of contaminated aerosol into other apartments via these routes could have transmitted the virus. Also, leaky sewage pipes could have allowed infectious aerosols of faecal material to escape into the narrow light well between the buildings. Although the primary mode of transmission is close contact with virus-contaminated droplets, preliminary studies have suggested that the virus may also be found in large quantities in urine and faeces from infected individuals.

Similar events may have taken place in other countries such as Vietnam, Singapore, and Toronto,[9,16] with unprotected healthcare workers being at the highest risk of virus infection.

In the absence of simple and rapid laboratory tests, the diagnosis of SARS is based on clinical features, and physicians should be aware of the disease's case definition which is set up by the WHO. Due to the rapidly increasing knowledge on SARS, the definition is updated periodically. The latest update categorized SARS into 'suspect' and 'probable' cases.[18]

The mortality of SARS differs between patient groups. In a retrospective case series of adult patients with probable SARS admitted to the intensive care unit (ICU) of a hospital in Singapore between 6 March and 6 June 2003, the primary outcome measure was the 28-day mortality after

symptom onset.[19] The mortality at 28 days for the entire cohort was 20 (10.1%) of 199 and for ICU patients 17 (37%) of 46, while the intensive care unit mortality at 13 weeks was 24 (52.2%) of 46.

In 115 patients diagnosed with SARS who were admitted to the Queen Elizabeth in Hong Kong, from March 2003, of whom 100 were either discharged or were dead at 31 May, crude mortality was 15.7% and 21-day mortality 10% (standard error 3%).[20] Multivariate analysis demonstrated that age >60 years (hazard ratio (HR) 3.5, 95%CI 1.2–10.2; $p=0.02$), the presence of diabetes mellitus or heart disease (HR 9.1, 95%CI 2.8–29.1; $p<0.001$), and the presence of other comorbid conditions (HR 5.2, 95%CI 1.4–19.7; $p=0.01$) were independently associated with the mortality. However, it was reported that only the presence of diabetes mellitus and/or cardiac disease (HR 7.3, 95%CI 3.1–17.4; $p<0.001$) was associated with adverse outcome as a whole.[20] Future studies with greater patient numbers will reveal the true SARS mortality and its relation to influenza or bacterial pneumonia mortality, but SARS-related critical illness seems to be very common.[21]

Aetiology

SARS is caused by a novel strain of coronavirus.[1–3] The group of coronaviruses is a member of the order of Nidovirales, a group of enveloped positive-sense RNA viruses. They synthesize a 3′ co-terminal set of subgenomic mRNAs in infected cells.[22,23] Coronaviruses are known to cause respiratory and gastrointestinal diseases in humans and domestic animals.[24,25]

Although the novel coronavirus strain has been identified, and significant progress has been reported for the development of a rapid diagnostic test, rapid reverse transcription (RT) polymerase chain reaction (PCR) tests are not widely available. Therefore, early management of suspected SARS cases is based on clinical presentation and epidemiological data of possible contact to patients with known SARS. Other diagnostic procedures include viral isolation and serum antibody tests. However, they cannot be used easily to confirm the diagnosis early in the course of the illness, and are only useful for epidemiological studies or retrospective confirmation. Among the initial patients admitted to the Prince of Wales Hospital with SARS,[8] more than 90% were subsequently confirmed to have evidence of infection with the SARS-associated coronavirus by RT-PCR or serum antibody analysis.

In a study testing clinical and post-mortem samples from 436 SARS patients in six countries for infection with SARS-CoV, human metapneumovirus, and other respiratory pathogens, SARS-CoV infection was diagnosed in 329 (75%) of 436 patients fitting the case definition of SARS; human metapneumovirus was diagnosed in 41 (12%) of 335.[26] Other respiratory pathogens were diagnosed only sporadically.

In another study, four cynomolgus macaques (*Macaca fascicularis*) were infected with SARS-CoV in an attempt to replicate SARS. All excreted SARS-CoV from nose, mouth, and pharynx from 2 days after infection, and three of the four developed diffuse alveolar damage similar to that in SARS patients. SARS-CoV was detected in pneumonic areas by virus isolation and RT-PCR, and was localized to alveolar epithelial cells and syncytia by immunohistochemistry and transmission electron microscopy.[26]

Clinical findings

Currently, the mean incubation period of SARS is estimated to be 6.4 days (95%CI 5.2–7.7), with a mean time from the onset of clinical symptoms to hospital admission varying between three and five days.[27] The main clinical features of the disease include initially common symptoms such as persistent fever, chills, myalgia, dry cough, headache, and dizziness. Less common initial symptoms include sore throat, sputum production, coryza, nausea or vomiting, and diarrhoea.[8,15] Watery diarrhoea has also been found in a subgroup of patients one week after the initial symptoms. This symptom was especially relevant in the cohort of patients infected by the 33-year-old male patient with chronic renal disease undergoing haemodialysis, described above.[28]

The clinical course of SARS appears to follow a bi- or triphasic pattern. The first phase, which represents the period of viral replication, is associated with an increasing viral load. Clinically, fever, myalgia, and other systemic symptoms occur, which generally improve after a few days. In phase 2, which represents an immunopathological imbalance, the major findings are the recurrence of fever, oxygen desaturation, and clinical and radiological progression of acute pneumonia. This phase is concomitant with falls in the viral load. The majority of patients respond to treatment in this phase, but about 20% may progress into phase 3. This phase is characterized by an acute respiratory distress syndrome (ARDS) which commonly necessitates mechanical ventilation. In comparison to adults,

SARS seems to be less aggressive in younger children, with no child requiring supplementary oxygen in one case series.[29]

Radiographic features

The radiographic findings of SARS share the common features of acute pneumonia.[30] In phase 1 of the disease with fever onset, almost 80% of SARS patients have abnormal chest radiographs that show airspace consolidation.

In a study which included four patients with a clinical diagnosis of SARS in Vancouver, BC, Canada, and eight patients from Hong Kong, the initial predominant radiographic findings in the patients at presentation were unilateral or bilateral ground-glass opacities ($n=5$), focal unilateral or bilateral areas of consolidation ($n=5$), and diffuse small nodular opacities ($n=1$).[31]

The chest radiographs also showed that two patients with consolidation also exhibited ground-glass opacities. One patient with a radiograph with predominantly ground-glass opacities also exhibited poorly defined small nodular opacities. Of the seven patients with ground-glass opacities, three radiographs had extensive and fairly symmetric bilateral opacities, one had bilateral and asymmetric opacities, two had unilateral opacities, and one had opacities only in the lower lobes of both lungs. In two patients, the areas of consolidation involved mainly the upper lung zones, in two other patients the lower zones, and the middle lung zones in one patient.

In one patient, the findings of the chest radiograph at admission were normal. A similar normal chest radiograph was also reported for a patient with SARS who developed haemorrhagic-fever-like changes.[32]

In another study, the opacities occupied a peripheral or mixed peripheral and axial location in 88% of patients.[33] More distinctive radiographic features of the disease were reported to be the predominant involvement of the lung periphery and the lower zone, in addition to the absence of cavitation, hilar lymphadenopathy, or pleural effusion.[33] During the second week of the disease course, a progression from unilateral focal airspace opacity to either multifocal or bilateral involvement was commonly present.[33] In one study, 12% of the patients developed a spontaneous pneumomediastinum and 20% of patients developed evidence of ARDS over a period of 3 weeks.[28] The incidence of barotrauma in intensive care unit admissions seems to be relatively high, despite low-volume, low-pressure ventilation. CT scan studies did not demonstrate excessive hyperinflation or bullous lung formation.[34] In this respect, high-resolution CT scans (HR-CT) may be useful to detect opacities in patients with normal chest radiographs. Within the HR-CT scans, the most common findings are ground-glass opacification, consolidation, and interlobular interstitial and intralobular septal thickening, with predominant involvement of the periphery and lower lobe. The peripheral alveolar opacities were similar to those found in bronchiolitis obliterans organizing pneumonia.[34]

Radiographical findings were also evaluated in the retrospective case series of 144 patients with SARS in the greater Toronto area.[15] Here, chest radiography on admission showed unilateral and bilateral infiltrates in 46% and 29% of patients, respectively. In 25% of individuals, no changes were found. Thirty-one percent of individuals (45/144) had progression of their pulmonary infiltrates while in the hospital, but 15 patients (10%) never developed signs of an infiltrate. Although there was variability in the pattern of the infiltrates (focal, lobar, diffuse), most patients had multifocal opacities, and 3% developed a pneumothorax while in the hospital.[15]

In the follow-up study of 75 patients from the community outbreak of SARS pneumonia,[28] the initial chest radiograph was reported to be pathological in 53 (71%) patients. In 37 (49%) patients, involvement was confined to one lung zone, and in 16 (21%) patients it was multizonal. Consolidation or lower-zone infiltrates occurred in 45 (60%) patients.[28] Initial high-resolution CT scans were performed in 33 (44%) patients; 18 (55%) had abnormalities confined to one lobe, while multilobar involvement was seen in 15 (46%). In eight (24%) patients, focal ground-glass opacification was the only type of abnormality, while 12 (36%) patients had consolidation only, and 13 (39%) displayed both types of infiltrates.[28]

Lung pathology

A first study on post-mortem tissue samples from six patients who died from SARS in February and March 2003 reported a diffuse alveolar damage, which was common but not universal.[35] Morphological changes included bronchial epithelial denudation, loss of cilia, and squamous metaplasia. In one case, secondary bacterial pneumonia was found, while a giant-cell infiltrate was found in four patients, with a pronounced increase in macrophages in the alveoli and the interstitium. In this respect, activated macrophages may play a prominent role for disease progression by liberating large amounts of

cytokines. The activation of macrophages may be less prominent in children, and therefore related to a milder form of the disease.

In two patients, a haemophagocytosis was present, and alveolar pneumocytes also showed cytomegaly with granular amphophilic cytoplasm. Electron microscopy revealed viral particles in the cytoplasm of epithelial cells corresponding to coronavirus. It was therefore concluded that SARS is associated with epithelial-cell proliferation and an increase in macrophages in the lung. It was suggested that the case definition of SARS should acknowledge the range of lung pathology associated with this disease. One full autopsy was performed in the study and found atrophy of the white pulp of the spleen.[35]

Similar findings were reported in a study on post-mortem lung sections from eight patients who died from SARS during the Spring 2003 Singapore outbreak. The predominant pattern of lung injury in all eight cases was diffuse alveolar damage.[36]

A further study reported autopsies of three patients who died of SARS.[37] In these post-mortem tissues, pulmonary lesions included bilateral extensive consolidation, desquamative pulmonary alveolitis and bronchitis, localized hemorrhage and necrosis, proliferation and desquamation of alveolar epithelial cells, exudation of protein and monocytes, hyaline membrane formation, lymphocytes and plasma cells in alveoli, and viral inclusion bodies in alveolar epithelial cells. Massive necrosis of splenic lymphoid tissue and localized necrosis in lymph nodes were also found. Further, signs of systemic vasculitis were present, including oedema, localized fibrinoid necrosis, and infiltration of monocytes, lymphocytes, and plasma cells into vessel walls of the lung, heart, liver, kidney and adrenal gland, and the stroma of striated muscles. There was also thrombosis in small veins and systemic toxic changes, including degeneration and necrosis of parenchymal cells of the lung, liver, heart, kidney, and adrenal gland. Electron microscopy examination showed clusters of viral particles, consistent with coronavirus, in lung tissue. It was concluded that SARS represents a systemic disease that injures many organs. Overall, the lungs, immune system, and systemic small vessels appeared the main targets of infection.[37]

Laboratory findings

Lymphopenia, with the destruction of both CD4 and CD8 lymphocytes, and features of low-grade disseminated intravascular coagulation, such as thrombocytopenia, elevated D-dimer levels, or prolonged activated partial thromboplastin time, are common features of SARS. Depending on the grade of airway tissue damage, elevated lactate dehydrogenase levels may also be found. Increases in creatinine kinase levels may reflect myositis.[8,15,16,28]

Diagnosis

The diagnostic criteria of SARS have been proposed by the Centers for Disease Control and Prevention

Table 1 Clinical criteria

Asymptomatic or mild respiratory illness
Moderate respiratory illness Temperature > 38°C and Clinical findings (1 +) of respiratory illness (e.g. cough, shortness of breath, difficulty breathing, hypoxia)
Severe respiratory illness Temperature > 38°C and Clinical findings (1 +) of respiratory illness (e.g. cough, shortness of breath, difficulty breathing, hypoxia) and Radiographic evidence of pneumonia, or Respiratory distress syndrome, or Autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause.

Table 2 Epidemiological criteria

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

(CDC). These criteria follow clinical, epidemiological, and laboratory features.[38]

Clinical criteria

Clinical criteria include (a) asymptomatic or mild respiratory illness; (b) moderate respiratory illness (e.g. temperature >100.4 °F/38 °C) and at least one more clinical finding of respiratory illness (e.g. cough, hypoxia, dyspnoea); (c) severe respiratory illness with clinical features of the second criterion and respiratory distress syndrome or radiographic evidence of pneumonia, or autopsy findings consistent with pneumonia, or the presence of respiratory distress syndrome without an identifiable cause (Table 1).[38]

Epidemiological criteria

Epidemiological criteria include travel that includes transit in an airport within 10 days of the onset of symptoms to an area with current, recently documented, or suspected community transmission of SARS, or close contact within 10 days of onset of symptoms with a person known or suspected to have SARS (Table 2).[38]

Laboratory criteria

The laboratory observations are separated into confirmed, negative or undetermined tests. Confirmed include: (a) the detection of an antibody to SARS-CoV in specimens obtained during the acute illness or >21 days after the onset of the illness; (b) detection of SARS-CoV RNA by RT-PCR, confirmed by a second RT-PCR assay using a second aliquot of the specimen and different PCR primers; or (c) the isolation of SARS-CoV.

Negative findings are the absence of antibody to SARS-CoV in convalescent serum obtained >28 days after symptom onset; undetermined cases are defined as laboratory testing either not performed or incomplete (Table 3).[38]

Case classification

Presently, case classification is separated into probable and suspected cases according to the CDC (Table 4).[38] A case of *probable SARS* is defined by the clinical criteria for severe respiratory illness of unknown aetiology, the epidemiological criteria for exposure and confirmed or undetermined laboratory criteria. A case of *suspect SARS* is defined by the

Table 3 Laboratory criteria

Confirmed
Antibody to SARS-CoV in specimens obtained during acute illness or > 28 days after illness onset, or
SARS-CoV RNA by RT-PCR, confirmed by a second PCR assay using a second aliquot of the specimen and a different set of PCR primers, or
Isolation of SARS-CoV
Negative
Absence of antibody to SARS-CoV in convalescent serum obtained > 28 days after symptom onset
Undetermined
Laboratory testing not performed or incomplete

Table 4 Case classification and exclusion criteria

Probable case
Meets the clinical criteria for severe respiratory illness of unknown aetiology and epidemiological criteria for exposure; laboratory criteria confirmed or undetermined.
Suspect case
Meets the clinical criteria for moderate respiratory illness of unknown aetiology, and epidemiological criteria for exposure; laboratory criteria confirmed or undetermined.
Exclusion criteria
A case may be excluded as a suspect or probable SARS case if:
An alternative diagnosis can fully explain the illness
The case has a convalescent-phase serum sample (i.e. obtained > 28 days after symptom onset) that is negative for antibody to SARS-CoV
The case was reported on the basis of contact with an index case that was subsequently excluded as a case of SARS, provided other possible epidemiological exposure criteria are not present

clinical criteria for moderate respiratory illness of unknown aetiology, and epidemiological criteria for exposure with confirmed, negative, or undetermined laboratory criteria.

Cases may be excluded as suspect or probable SARS case if an alternative diagnosis can fully explain the illness, or the case was reported on the basis of contact with an index case that was subsequently excluded as a case of SARS (e.g. another aetiology fully explains the illness) if other possible epidemiological exposure criteria are not present.[38] In particular, other bacterial or virus-induced forms of pneumonia have to be excluded by standard laboratory tests. (i.e. pneumococcal or *Legionella* antigen tests in urine specimen).

The WHO has also stated that as SARS is currently a diagnosis of exclusion, the status of a reported case may change over time.[39] Therefore, patients should always be managed as clinically appropriate, regardless of their case status. It is stated that: (i) cases initially classified as suspect or probable, for whom an alternative diagnosis fully explains the illness, should be discarded after carefully considering the possibility of co-infection; (ii) a suspect case who, after investigation, fulfils the probable case definition should be reclassified as 'probable'; (iii) a suspect case with a normal CXR should be treated as deemed appropriate, and monitored for 7 days—those cases in whom recovery is inadequate should be re-evaluated by CXR; (iv) those suspect cases in whom recovery is adequate but whose illness cannot be fully explained by an alternative diagnosis should remain as 'suspect'; (v) A suspect case who dies, on whom no autopsy is conducted, should remain classified as 'suspect', but if this case is identified as being part of a chain of SARS transmission, it should be reclassified as 'probable'; (vi) if an autopsy is conducted and no pathological evidence of RDS is found, the case should be discarded.[39]

Conclusions

The recent worldwide onset of the SARS epidemic has initiated a rapid and successful collaboration between laboratories, which have examined and elucidated the causative agent of the epidemic and analysed its epidemiological features.

However, the development of early diagnostic tests and an effective treatment is still needed, and therefore, the global collaboration of clinicians and scientists continues. With the availability of the genome sequence of the SARS-CoV, the development of vaccines and antiviral agents will be made easier, as there is no established therapy to date. Although corticosteroids may be useful after day 7, first side-effects such as fatal aspergillosis in a patient with SARS who was treated with corticosteroids have already been reported.[40]

The WHO continues to consolidate global surveillance data for the outbreak period 1 November 2002 to 5 July 2003, and even now, in a situation of no new cases of SARS, the disease remains a major respiratory health hazard. Parallel to influenza virus outbreaks, new epidemics may arise at the end of the year. Clinical, experimental and epidemiological research is required to control the disease, and physicians should be alert to the possibility of new cases of SARS in autumn, winter or spring.

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