Chapter 17
The Future of Severe Acute Respiratory Syndrome

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Introduction

The passage of time has healed some of the wounds inflicted by the deadly epidemic. The economy in Hong Kong and most of Asia has picked up and the communities have gone back to their daily activities. The masks and the gloves are off and people have gone back to their old habits with respect to personal hygiene and work practices. After all, old habits diehard.

However, SARS continues to lurk in the background and still causes a diagnostic dilemma. By the end of 2003/early 2004 (at the time of writing this chapter), there were five sporadic cases of SARS, two involving laboratory researchers and three outside the laboratory in Guangdong province in China. Although the two laboratory cases (Taiwan, Singapore 1) were readily identified, the cases in Guangdong were definitively verified more than a week after the suspicion was raised. The clinical parameters, laboratory tests and history of contact in this patient were initially nebulous, highlighting the difficulty in the early diagnosis of this potentially fatal disease. Despite detailed contact tracing the source of the infection was not definitively traced and it has been postulated that the source might have been civet cats as unpublished reports from Guangdong and Hong Kong have found similarities in the genetic sequences of the virus in the SARS patient and civet cats, which is a gourmet delicacy in Southern China. Based on this assumption the local authorities in Guangdong undertook a controversial cull of 10,000 civet cats. The WHO cautioned against the move saying there was no convincing evidence that the patients had been in direct contact with wild animals (one of the patients worked in a restaurant which had civet cats on its menu). The WHO has also expressed concerns that the mass slaughter of civet cats could destroy evidence of origin in tracing the SARS virus. Reports from China have also found DNA traces of the SARS in rats and local authorities in Guangdong are planning a large extermination program against rats in the city.

In all the cases, the patient and their contacts were swiftly isolated and quarantined by the local public health authorities. As a result no further transmission appears to have occurred and the local authorities were commended for their efforts in limiting the disease spread by the WHO.

These cases highlight several issues regarding SARS in the post-epidemic period:

1. the difficulty in early diagnosis of the disease in the post-epidemic period. During the previous outbreak the diagnosis was predominantly clinical. If a patient presented with clinical symptoms, positive chest X-Ray and history of contact with SARS patient the diagnosis was SARS. However, in the post outbreak situation the diagnosis is based
predominantly on a series of laboratory tests which are time consuming and by the
time the definitive diagnosis is established patient become asymptomatic.
2. health-care workers will continue to be at risk of infection
3. infection control and safe practice are of prime importance
4. a well-planned protocol for disease surveillance and notification, public health alert
system and contact isolation/quarantine can work very well in limiting the disease.

**Key Points**
- sporadic cases were occurring after the end of the epidemic
- some cases had no apparent source
- laboratory tests take time for confirmation
- healthcare workers remain at risk of infection

On the other hand, in view of issues arising from the after-effects of SARS (lung scarring,
avascular necrosis of bones, psychological trauma to healthcare workers, patients and their
families), a well thought out future treatment plan and research protocols would also help
to reduce future damage should we have to deal with the disease again. If one is to learn
from past-experiences, in addition to early and accurate diagnosis, the following issues
will have to be addressed:
- randomized controlled trial(s) on different diagnostic tests (including radiology)and
treatment regimes
- plan of action for the community (isolation, quarantine, immigration) and hospitals
This chapter hopes to update the readers with the new case definition of SARS and the
procedures put in place to deal with any recurrence of SARS on a global scale.

**Diagnosis and Classification**

**CDC Case Definition**

Less than a week prior to the sporadic case in Taiwan, the Centers for Disease Control and
Prevention of the United States (CDC) issued an Updated interim U.S. case definition for
SARS.

A) **Clinical Criteria**

- **Early illness**: Presence of two or more of the following features: fever (might be
subjective), chills, rigors, myalgia, headache, diarrhea, sore throat, or rhinorrhea
• **Mild-to-moderate respiratory illness:** Temperature of $>100.4^\circ\text{F} (>38^\circ\text{C})$* and one or more clinical findings of lower respiratory illness (e.g., cough, shortness of breath, or difficulty breathing)

• **Severe respiratory illness:** Meets clinical criteria of mild-to-moderate respiratory illness and one or more of the following findings:
  - Radiographic evidence of pneumonia, or
  - Acute respiratory distress syndrome, or
  - Autopsy findings consistent with pneumonia, or acute respiratory distress syndrome, without an identifiable cause.

**B) Epidemiologic Criteria**

• **Possible exposure** to SARS-associated coronavirus (SARS-CoV)
  One or more of the following exposures in the 10 days before onset of symptoms:
  1. Travel to a foreign or domestic location with documented or suspected recent transmission of SARS-CoV or
  2. Close contact with a person with mild-to-moderate or severe respiratory illness and history of travel in the 10 days before onset of symptoms to a foreign or domestic location with documented or suspected recent transmission of SARS-CoV

• **Likely exposure** to SARS-CoV
  One or more of the following exposures in the 10 days before onset of symptoms:
  1. Close contact with a person with confirmed SARS-CoV disease or
  2. Close contact with a person with mild-to-moderate or severe respiratory illness for whom a chain of transmission can be linked to a confirmed case of SARS-CoV disease in the 10 days before onset of symptoms.

**C) Laboratory Criteria**

Tests to detect SARS-CoV are being refined and their performance characteristics assessed; therefore, criteria for laboratory diagnosis of SARS-CoV are changing. The following are general criteria for laboratory confirmation of SARS-CoV:

• Detection of serum antibody to SARS-CoV by a test validated by CDC (e.g., enzyme immunoassay), or

• Isolation in cell culture of SARS-CoV from a clinical specimen, or

• Detection of SARS-CoV RNA by a reverse transcription polymerase chain reaction test validated by CDC and with subsequent confirmation in a reference laboratory (e.g., CDC).
D) **Exclusion Criteria**
A case may be excluded as a **SARS report under investigation** (SARS RUI), including as a CDC-defined probable SARS-CoV case, if any of the following apply:

- An alternative diagnosis can explain the illness fully, or
- Antibody to SARS-CoV is undetectable in a serum specimen obtained >28 days after onset of illness, or
- The case was reported on the basis of contact with a person who was excluded subsequently as a case of SARS-CoV disease; then the reported case also is excluded, provided other epidemiologic or laboratory criteria are not present.

E) **Case Classification**

1. **SARS report under investigation**
   Reports in persons from areas where SARS is not known to be active
   - **SARS RUI-1**: Cases compatible with SARS in groups likely to be first affected by SARS-CoV if SARS-CoV is introduced from a person without clear epidemiologic links to known cases of SARS-CoV disease or places with known ongoing transmission of SARS-CoV
   - Reports in persons from areas where SARS activity is occurring
   - **SARS RUI-2**: Cases meeting the clinical criteria for mild-to-moderate illness and the epidemiologic criteria for possible exposure (spring 2003 CDC definition for suspect cases)
   - **SARS RUI-3**: Cases meeting the clinical criteria for severe illness and the epidemiologic criteria for possible exposure (spring 2003 CDC definition for probable cases)
   - **SARS RUI-4**: Cases meeting the clinical criteria for early or mild-to-moderate illness and the epidemiologic criteria for likely exposure to SARS-CoV

2. **SARS-CoV disease**
   - **Probable case** of SARS-CoV disease: meets the clinical criteria for severe respiratory illness and the epidemiologic criteria for likely exposure to SARS-CoV
   - **Confirmed case** of SARS-CoV disease: clinically compatible illness (i.e., early, mild-to-moderate, or severe) that is laboratory confirmed

Further definition of the above terms is available at the CDC website.

**WHO Case Definition**
Prior to the sporadic case in Singapore, on 14th August 2003, the World Health
Organization (WHO) also modified their case definition for SARS in an article titled “Alert, verification and public health management of SARS in the post-outbreak period” 3. This modified clinical case definitions is as follows:

- A person with a history of fever (\( \geq 38^\circ C \))
- One or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath)
- Radiographic evidence of lung infiltrates consistent with pneumonia or RDS OR
- Autopsy findings consistent with the pathology of pneumonia or RDS without an identifiable cause.

For a sporadic outbreak or the early days of an epidemic, it may be difficult to use the epidemiological criteria for the diagnosis of SARS since sporadic cases are unlikely to provide history of contact. On the other hand, the lack of a rapid and accurate biochemical test for the detection of SARS-CoV in the first few days of the illness 2,4 excludes use of the laboratory criteria early in the disease. Thus, one is again left with relying on the clinical criteria for early diagnosis.

**Key Points**

- New case definitions released by the CDC and WHO in the post-epidemic period
- Clinical signs and radiographic confirmation constitute the main elements in early diagnosis
- CDC definition is extensive and covered various different situations

**Prominence of Radiology**

In both revised case definitions, radiographic findings have been included as part of the clinical case definition and diagnostic workup by the CDC and WHO 2,4,5. Such reliance on imaging demands a high sensitivity from whichever imaging modality is chosen. At
present, Computed Tomography (CT) has the highest sensitivity in the demonstration of lung abnormalities. A study by Wong et al.\textsuperscript{6} has shown that this high sensitivity was also true for the early detection of “occult” lung abnormalities in SARS patients. Therefore, CT should be used as a close second line investigation after an initial normal chest radiograph in the workup of a suspected SARS patient as recommended by the CDC\textsuperscript{4}. The significance of an early and accurate diagnosis in the quarantine of disease and effecting early treatment cannot be overstated.

The revised WHO clinical case definition is narrower in scope compared its previous definition in the sense that it does not include patients who present with no fever or with minimal chest symptoms, or with gastrointestinal symptoms (see Amoy Gardens SARS outbreak\textsuperscript{7}) as compared to the broader CDC clinical definition\textsuperscript{2}. On the other hand, an all-encompassing case definition may increase the number of false positives and place a considerable load on health resources and increase the public anxiety.

\textbf{Key Points}

- Radiology continues to be a major diagnostic tool
- CT should be performed early when in doubt

\textbf{Clinical Trials}

During the epidemic, radiology played an important role in the initial diagnosis, in progress monitoring and assessment of treatment effect, and in the detection of complications and treatment side effects. All of these parameters were retrospectively analyzed for the patients after the epidemic and useful results have emerged. For the next outbreak, prospective trials have to be considered and forward planning is necessary. Similarly, the treatment of SARS has been controversial and well-designed clinical trials are essential to settle the differences.

A. Treatment trials

Two major agents have been used in the treatment of SARS during the epidemic, namely antivirals and corticosteroids. The treatment remained controversial particularly due to the lack of a randomized controlled trial using either agent. The emergence of possible side-effects (psychosis, cardiac arrhythmia) and complications (secondary infections, avascular necrosis) have made the issue of treatment choice even more difficult. On the other hand,
other drugs such as Kaletra show some promising results. Therefore, it is essential that a double blinded, randomized controlled trial be in place for the next outbreak.

B. Imaging trials
The sensitivity and specificity of imaging in the diagnosis of SARS have not been established. This is probably the most important contribution imaging could provide for the management of the disease. Future studies on this will have to establish this in a double blind trial where all patients with fever and lower respiratory tract symptoms (as per the current WHO case definition) are imaged and diagnosed to have SARS or not.

The use of early imaging signs as predictors of prognosis is an attractive option. Previous studies have suggested that the percentage of lung volume involvement and the number of lesions may be useful predictors. Although the results appear intuitive, the study was done retrospectively and suffers from treatment bias (progressive chest radiograph deterioration would have caused the clinicians to step up treatment). A future trial should put this into practice prospectively and a blinded randomized controlled trial on treatment should take this into account as one of the parameters for assessment.

Key Points
- Clinical trials valuable and essential if SARS recurs
- Both treatment and imaging efficacy need to be evaluated
- Imaging may provide an early indication to prognosis

Plans for the Future
For sporadic cases, time is of the essence to avoid an outbreak. The diagnosis needs to be established rapidly to allow confinement of the contacts and isolation of the patient. Hospitals and health organizations have been encouraged by the WHO to set up surveillance systems and early warning protocols.

A. Plans on a global scale
The reappearance of SARS in the human population would be considered a global public health emergency. Therefore surveillance is of utmost importance. The WHO has designated three levels of surveillance for SARS for different regions in the world based on their previous level of exposure. These are defined as:
(1) **Potential zone of re-emergence** of SARS-CoV. Identified as source(s) of the previous outbreak in November 2002 or areas with an increased likelihood of animal to human transmission of SARS-CoV infection;

(2) **Nodal areas** where sustained local transmission experienced during the previous outbreak or entry of large numbers of persons from the potential zone of re-emergence of SARS-CoV.

(3) **Low risk areas.** Never reported cases, reported only imported cases or experienced only limited local transmission during the previous outbreak.

Based on this, WHO recommends the following staged approach to surveillance (summarized in Table 1):

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<th>Potential zone of re-emergence</th>
<th>Nodal areas</th>
<th>Low risk areas</th>
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<td>SARS Alert</td>
<td>Y</td>
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<td>Enhanced surveillance for SARS</td>
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<td>Special studies for SARS-CoV infections in animal and human populations</td>
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The SARS Alert:
For the purposes of SARS surveillance (expedite diagnosis, step up infection control, activate the public health response and raising a global alert), the WHO has devised the SARS alert 3. When this alert is present, appropriate infection control and public health measures against SARS should be implemented until SARS has been ruled out as a cause of the atypical pneumonia or respiratory distress syndrome.

The SARS alert is defined as:

I. Two or more health care workers in the same health care unit fulfilling the clinical case definition of SARS (see new case definition described above) and with onset of illness in the same 10-day period.

OR

II. Hospital acquired illness in three or more persons (health care workers and/or other hospital staff and/or patients and/or visitors) in the same health care unit fulfilling the clinical case definition of SARS and with onset of illness in the same 10-day period.
B. Plans for the Community

For each region, the WHO recommends a plan for infection surveillance and control to be adapted based on its guidelines. The following should be included in such a plan:

1. rapid diagnosis
2. immediate isolation of the infected patient(s)
3. proper isolation facilities
4. contact tracing and quarantine
5. surveillance of high risk institutions/ populations (hospitals, nursing homes etc.)

In line with the WHO recommendations, the Hong Kong government has developed a three level response system:

- Alert Level Response - activated when there is a laboratory-confirmed SARS case outside Hong Kong; or a SARS Alert in Hong Kong.
- Level 1 Response - activated when there is 1 or more laboratory-confirmed SARS cases in Hong Kong occurring in a sporadic manner.
- Level 2 Response - activated when there are signs of local transmission of the disease in Hong Kong.

In addition, the following measures will be undertaken:

1. A steering committee will be set up to oversee disease control and co-ordinate measures to limit the socio-economic effects of an epidemic. Disaster drills will be conducted to test the surveillance system and response strategies.
2. A centre for disease control will be set up to speed up laboratory tests, strengthen contact tracing and disease investigations. Communication is another important aspect of disease control. In Hong Kong, the public health authority and the government will keep close contact with Mainland China and neighboring health authorities to ensure information exchange.
3. As in other international ports, temperature screening with infra-red scanners and health declarations will continue to be operated at immigration check points.

Aside from providing a robust system of disease surveillance and a clearly defined response system, the WHO has recommended vaccination against influenza be encouraged to minimize this common disease from the differential diagnosis of SARS. Healthcare workers in particular should all be vaccinated and those who do develop the “flu” should be encouraged to stay at home, rather than to soldier on, to avoid spreading this mimicker of SARS.
While the WHO and regional public health authorities will continue to monitor the disease and co-ordinate communication, there is another very effective channel of communication among medics, healthcare workers and the public. The Internet has been an invaluable platform in disseminating news and information to the whole world. Our radiology department has had some success with our SARS webpage in providing radiographic images of SARS. The World Wide Web will continue to play an important role in the fight against SARS.

Television advertising campaigns have been continually launched by the government to 1) promote cleanliness and vigilance; 2) keep the public informed of preparations being made against a second outbreak; 3) advertise to visitors that the city is once again safe.

C. Plans for the Hospitals
Isolation wards, and in some centers infectious disease wings, have been built since the end of the epidemic. Additional 530 isolation rooms with 1280 beds in total were added in nine major hospitals in Hong Kong. Different levels of infection control measures are in place to be stepped up to meet the level of suspicion (Figures. 1 and 2). Protective clothing and resources have been replenished to meet a drawn out epidemic (3 months supply). Protection during transport of patients is being put into place. These are all essential preparations that need to be laid down before the next outbreak.

In Hong Kong, a three-tier response plan has been established by the Hospital Authority to be used in the event of a major outbreak of infectious disease, including Severe Acute Respiratory Syndrome (SARS):
- **Green Alert (prior to Alert Level Response):**
  Hospital alerted to an abnormal pattern of infectious disease in the community or inside the hospital system and when there are existing guidelines and knowledge on treatment and control, and local action is judged to be adequate.
- **Yellow Alert (Level 1 Response):**
  The hospital is alerted to an abnormal pattern of infectious disease, which may have territory-wide implications, or require a HA-wide response in:
  A. providing central coordination in data collection and interpretation of the epidemiological pattern.
  B. refining clinical management or infection control guidelines.
C. mounting a territory-wide response in service management and resource deployment.

- Red Alert (Level 2 Response):
  Higher-level inter-departmental response will be required and the Government may activate the Inter-departmental Action Coordinating Committee. In a major disaster situation, there will be a need for strategic command to effect prompt and decisive response. There will need to be a mechanism to mobilize resources (supplies and the population is protected.

The plan provides a detail description of the response actions, staff deployment, patient allocation and distribution of resources. A system to monitor healthcare workers’ sick leave in all hospitals is in place to monitor for unusual patterns. All staff are required to report fever, flu-like symptoms to hospital management. E-SARS, an electronic database will be expanded for use in surveillance and monitoring of infectious diseases.

D. Plans for Radiology departments

The chest radiograph with its inherent blind areas will not be able to pick up all early cases. Thin section CT will have to be performed on these suspicious patients if the chest radiograph is negative. This is particularly important as the laboratory tests have yet to achieve a high sensitivity in the early stages of the disease.

Given that sporadic cases are likely to herald an outbreak and that these cases will be radiographed with other lower respiratory tract infection patients, work practices may have
to be modified. Specific time slots should be cleared for imaging these suspicious cases, preferably at the end of the day when the department is not crowded and more time and attention could be spent on infection control. Different levels of infection control have to be devised to correspond to the different levels of SARS alert. Education on and supervision of infection control measures should be continued.

Reporting practices may also have to be modified. Unusual radiographic trends (atypical pneumonia) need to be monitored as a possible indicator of disease outbreak. Decreasing film transport, limiting handling/transporting of ward examination requests and patient would help reduce contamination during the epidemic (Figures. 3 and 4). Obviously a PACS system solves a lot of these problems, but with limited resources, the problems could still be overcome with some planning e.g. immediate reporting, faxing of requests, mobile/satellite radiographic examination units.

**Key Points**
- Plans were drawn up for all levels of society
Effectiveness of various plans rest on individuals carrying out their designated roles

Daily practices for all need to be changed to compliment the plans

Education, surveillance and communication are important

Conclusion

The knowledge on SARS is continuously evolving and being updated on a daily basis. It is essential that health care workers are familiar with the updated information and the knowledge acquired should be put into use if a future outbreak is to occur. Prospective clinical trials and public health protocols need to be planned taking past experience into account. Radiology will continue to play a major role in the diagnosis and assist in the treatment of patients.
Chapter 17

The Future of Severe Acute Respiratory Syndrome

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References


