Emerging Infectious Disease (3): Severe Acute Respiratory Syndrome

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Abstract

First recognized in late February 2003, severe acute respiratory syndrome (SARS) was successfully contained in less then 4 months. SARS is responsible for the first pandemic of the 21st century. After first appearing in Gunagdong in mainland China, it spreaded to 29 countries, affected more than 8000 patients and caused 774 deaths. The major clinical features include persistent fever, myalgia, malaise, dry cough, headache, and dyspnea. Common laboratory features include lymphopenia, thrombocytopenia, raised alanine transaminases, lactate dehydrogenase, and creatine kinase. Fever is the most common symptom on presentation, however, older subjects and patients with comorbids may have atypical symptom. The combination of compatible clinical, radiological and laboratory findings should alert the physicians on making the diagnosis of SARS. Management of SARS focuses on prevention and containment of spreading. Treatment protocols including antiviral agents, steroid and ventilator use are still controversial. In the absence of a vaccine, the most effective way to control a new viral disease such as SARS is to break the chain of transmission, which is accomplished via good basic public health measure and infection control measures.*(Ann Disaster Med. 2005;3 Suppl 2:S52-S66)*

Key words: SARS; Emerging Disease; Surveillance

Introduction

First recognized in late February 2003, severe acute respiratory syndrome (SARS) was successfully contained in less then 4 months. On 5 July 2003, WHO reported that the last human chain of transmission of SARS had been broken. In the 4 month epidemic period, more then 8000 probable cases were reported in 29 countries and regions with a death toll of 774.[1] (Table 1)

A novel corona virus has been identified as the pathogen responsible for SARS.[2-4] Fever followed by a rapidly progressive respiratory compromise that may lead to the requirement of mechanical ventilation and intensive care is the key complex of the syndrome. From its rapid development and severity of infection, SARS is compatible with the Black Death Disease – the plaque of the 13th century. Due to the coordinated response to SARS by the medical and scientific community, it urged un-

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derstanding and control of epidemic rapidly. The outbreak of SARS demonstrates dramatically the global havoc that can be wreaked by a newly emerging infectious disease.

Spreading of the Disease

The early cases of SARS appeared to have originated in southern China. In November 2002, reports of a high contagious severe atypical pneumonia began to emerge from Guandong Province.[5] The condition was particularly prevalent among healthcare workers and members of their household. Many cases were rapidly fatal.[5] Local health officials reported 305 cases and 5 deaths of the unknown disease to the WHO at 9 February 2003. Chinese Ministry of Health informed the WHO that the outbreak in Guandong consisted with atypical pneumonia. Further investigations rule out anthrax, pulmonary plague, leptospirosis ,and hemorrhagic fever. Chlamydia pneumonia was once believed to be the culprit according to the report of Chinese Ministry of Health presented at the end of February 2003.[6-7] Retrospective analysis of 55 cases in Guangzhou showed positive antibodies to SARS CoV in 48. Genetic analysis showed that the SARS CoV isolated from Guangzhou shared the same origin with those in other countries, with a phylogenetic pathway that matched the spread of SARS to other parts of the world.[8]

SARS was carried out of Guandong Prov-

Table 1. Summary table of areas that experienced local transmission of SARS during the outbreak period from 1 November 2002 to 31 July 2003

Country	Area	From	To
Canada	Greater Toronto Area	23-Feb-03	2-Jul-03
Canada	New Westminster (within the Greater Vancouver Area)	28-Mar-03	5-May-03
China	Beijing	2-Mar-03	18-Jun-03
China	Guangdong	16-Nov-02[f]	7-Jun-03
China	Hebei	19-Apr-03	10-Jun-03
China	Hong Kong Special Administrative Region	15-Feb-03	22-Jun-03
China	Hubei	17-Apr-03	26-May-03
China	Inner Mongolia	4-Mar-03	3-Jun-03
China	Jilin	1-Apr-03	29-May-03
China	Jiangsu	19-Apr-03	21-May-03
China	Shanxi	8-Mar-03	13-Jun-03
China	Shaanxi	12-Apr-03	29-May-03
China	Tianjin	16-Apr-03	28-May-03
China	Taiwan	25-Feb-03	5-Jul-03
Mongolia	Ulaanbaatar	5-Apr-03	9-May-03
Philippines	Manila	6-Apr-03	19-May-03
Singapore	Singapore	25-Feb-03	31-May-03
Vietnam	Hanoi	23-Feb-03	27-Apr-03

http://www.who.int/csr/sars/areas/areas2003_11_21/en/print.html
Data reported from WHO website

ince on 21 February 2003, when an infected 64 year old nephrologist visited Hong Kong. He spent a single night on the 9th floor of a hotel and was admitted to a hospital on 22 February. Ten days later, he died of severe pneumonia. At least 16 hotel guests and visitors had been infected by the nephrologist. As a result of the relatively long incubation period of 10-14 days in some cases, SARS spreaded rapidly and globally by international traveling to their destined cities without any symptoms before their arrival. This is believed to have been the source of infection causing subsequent outbreaks of SARS in Hong Kong,[9,10] Vietnam,[11] Singapore,[12] Taiwan,[13] and Canada.[35] These countries then became the hot zones of the disease, characterized by rapid increased in the number of cases, especially in healthcare workers and their close contacts. In these areas, SARS first appears in the hospital settings, where healthcare workers exposed themselves to the infectious agent without barrier protection due to unawareness that a new disease had surfaced. All of these initial outbreaks were subsequently characterized by chains of secondary transmission outside the healthcare environment and caused further spreading in community.[10, 14-15]

On 28 February 2003, Dr Carlo Urbani, a WHO official based in Vietnam, was alarmed by these cases of atypical pneumonia in the French Hospital, where he has asked to assist. He is concerned it might be avian influenza and notified the WHO Regional Office for the Western Pacific. Following mounting reports of cases among staff in the Hanoi and Hong Kong hospitals, WHO issued a global alert about cases of severe atypical pneumonia on 12 March.[6] The alert was heightened after cases were also identified in Singapore and Canada. Travel advisory was also included in the alert issued on 15 March, which advising all individuals traveling to affected areas to be watchful for the development of symptoms for a period of 10 days after returning.[16] A new coronavirus was identified on 24 March, its sequence was determined on 12 April. Laboratory method including serological tests and reverse-transcriptase polymerase chain reaction (RT-PCR) were developed for case identification.[2-3,17] Case definition was also published by CDC and WHO. On 5 July 2003, WHO announced that the last known chain of human-to-human transmission of the SARS CoV had been broken in Taiwan, which brought an end to the initial outbreak of SARS.[18]

Epidemiology

From all the statistics and epidemiologic studies, SARS-CoV is less transmissible than was initially thought.[19] Outbreak have been restricted to families who lived in high density accommodation, hotels and hospitals. This spreading character is the hallmark of a virus with low communicability. It is predominantly spread in droplets that are shed from the respiratory secresions of infected persons.[20] The use of aerosol-generating procedures (e.g. aerosolized medication, non-invasive positive ventilation mask, bronchoscope, endotracheal intubation and sputum suction) in hospital may facilitate the transmission of SARS CoV.[20-25] Fecal or airborne transmission is less frequent and happened only in specific circumstance.[17] No report about vertical or perinatal transmission was made. Most patients might not effectively transmit the virus. During outbreak in Singapore, 162 (81%) individuals of all prob-

able SARS cases had no evidence of transmission of a clinically identifiable illness to other persons.[26] Numbers of secondary infections was 2.7 on average per case at the start of Hong Kong epidemic.[19] Transmission rate fell during the epidemic after public health and other controlling measures were taken. However, there are few infected persons – "superspreaders" have been responsible for a disproportionate number of transmission.[26-28] Superspreaders and nosocomial amplification were the main factors that leading to the 2003 outbreak of SARS. There was no documented isolation of the virus from persons with asymptomatic infections. In all serologic and epidemiologic studies, transmission from asymptomatic cases cannot be proved.[27, 29] Transmission from probable cases to healthcare workers took place generally on five or more days after the symptom onset.[23, 28, 30] This correlate with reports that viral load detected by RT-PCR is 2.3 X 10^5 copies per ml on day 5 and then reach its peak on day 10 with a mean geometric value of 1.9 X 10^7 copies per ml of nasopharyngeal aspirates.[17]

Put all these facts together, SARS-CoV is sufficiently transmissible to cause an epidemic of great extent if it is left unchecked. With good basic public health measure and infection control measures , it is not so contagious and uncontrollable.[31]

The incubation period of SARS estimated form a single point of exposure is between 2-10 days with a median ranging form 4-7 days.[23-25] One study in China reported that some cases may have longer incubation period (20 days), but the data on the history of exposure were incomplete.[32] The mean time from onset of clinical symptoms to hospital admission varied between 3-5 days.[28] Suggestions on public health measures provided by WHO use a 10 days period for observation were successful in breaking the chain of global infection.

Mortality of SARS was estimated by WHO initially between 0-50% : 1% in persons aged 24 years and younger ; 6% in persons aged 25-44 years ; 15% in persons aged 45-64 years ; and greater than 50% in persons aged 65 years and older.[33] It varies from 3% - 15% in different studies. According to WHO statistics, the fatality of SARS ranged from 11-17% in Hong Kong, from 13-15% in Singapore, from 15-19% in Canada and from 5-13% in China.[1, 28, 33] Treatments, clinical presentations, laboratory studies and patient characters were used to predicting the risk of mortality.[9, 14, 17, 34]

Clinical Features

The initial symptoms of SARS are non-specific, making correct diagnosis of SARS patient difficult. Some features of the history, physical examination, laboratory findings and results of radiological examinations, however, should alert physicians to add SARS as a differential diagnosis.

The major clinical features on presentation include persistent fever, chills, myalgia, malaise, dry cough, headache and dyspnea.[8-9, 17, 35-38] The most common symptom in SARS patients is fever with a body temperature > 38 ℃.[8-9, 39] Fever is therefore a main criteria in the WHO case definition of suspected or probable SARS. However, fever may be absent during early stage of SARS CoV infection. In the elderly or patients with comorbidities or impaired immune function, absent of fever is not reliable to rule out SARS. In such patients, the pre-

senting problem may be a fall and fracture.[39-40] Fever is often associated with other symptoms such as chills, headache, malaise, myalgia and dizziness. In studies of different cohorts, fever present in 94-100% of patients with SARS.[8-9, 36-38] Cough is common, but shortness of breath, tachypnea, or respiratory distress is prominent only in the later stage of the illness.[37-38] Unlike other atypical pneumonia caused by mycoplasma or chlamydia, upper respiratory symptoms such as coryza, rhinorrhea or sore throat are less common. Sputum production is also rare.[9, 14] Wheezing is generally absent.[36-38] Fever associated with watery diarrhea was reported in 73% of patients 7 days after onset of clinical symptoms in the Amoy Gardens outbreak.[17] The diarrhea was described as watery in large volume but contained no blood or mucus. The frequency of diarrhea was 6 +/- 4 times per day and the duration was 3.9 +/- 2.3 days. Viral shed and faulty sewage system may responsible for the transmission of SARS CoV via fecal-oral route.[41] Diarrhea was less common in published studies performed base on other cohort. It is unknown to what extent asymptomatic infections can occur.

Laboratory Findings

Lymphocytopenia, thrombocytopenia, prolonged activated partial thromboplastin time, raised D-dimer (presentation of disseminated inavascular coagulation) , raised lactate dehydrogenase, alanine transaminases, and creatine kinase are common laboratory features of SARS.[8-10, 17, 35-38]

Progressive lymphocytopenia was found in 98% of patient in one study and reaching its lowest point in the second week. The lymphocyte count recovered in the third week, with 30% of patients still being lymphopenic by the fifth week after symptom onset. Most Patients had reduced CD4 and CD8 T cell count during the early phase, with mean CD4 and DC8 T cell count of 287 cells/ì l (normal : 410 to 1590 cells/ì l) and 242 cells/ì l (normal : 62 to 559 cells/ì l) , respectively.[47] Low CD4 and CD8 lymphocyte counts at presentation were associated with an adverse outcome in one study.[42]

Fifty percent of patients developed a self-limiting thrombocytopenia. The degree of thrombocytopenia was mild (platelet counts > 50000/ì l), and reached its low point at first week. No patient had major bleeding or required platelet transfusion in the study.[42] Transient leucopenia was found in 64% of patients during first week after symptom onset. 61% of patients developed leucocytosis during the second and third week of illness.[42] Decrease in left ventricular ejection fraction associated with raised lactate dehydrogenase and creatine kinase was reported. Exact mechanism is unknown.[43] Mild raise in aminotransferase levels was reported in 23-50% of SARS patients. Clinical pathological significance is unclear.[9-10] Studies suggest that immune mediated process is responsible for the raised aminotransferase level.[44]

Some studies connect raised lactate dehydrogenase and aminotransferase with extensive lung injury. It is possible that these abnormal laboratory findings may be also, at least partially, secondary to hemolytic effects of ribavirin treatment. In a multivariate analysis, elevated LDH was an independent predictor for poor outcome in SARS patients.[44]

There are several reports on atypical clinical presentation of SARS. Patients may present

without fever, or with diarrhea but no pneumonia. Due to no reliable rapid diagnostic tests in the early stage, identifying SARS patients with atypical presentation is difficult. Fisher et al. described four patients with atypical presentations who were later diagnosed with SARS. All of them were afebrile on presentation. However, the four patients all showed lymphocytopenia and raised lactate dehydrogenase.[39] These laboratory findings could alert physicians in making the diagnosis of SARS.

In many viral diseases, viral shedding is greatest during the early symptomatic phase. However, virus shedding is comparatively low during the initial phase of SARS.[17] The detection rates for SARS CoV using conventional RT-PCR are low in the first week of illness.[45] The positive rates on urine, nasopharyngeal aspirate, and stool specimen have been reported to be 42%, 68%, and 97% respectively on day 14 after symptom onset.[17] Sensitivity of nasopharyngeal specimen can reach 80% for the first 3 days by improvement on methods of extracting specimens and applying quantitative real-time RT-PCR techniques.[46] The detecting rates by quantitative real-time RT-PCR for SARS CoV RNA in blood specimen was reported to be 80% as early as day 1 of hospital admission but then drop to 75% and 42% on day 7 and day 14 respectively.[47] Serological test by detecting IgG seroconversion to SARS CoV may take 28 days to reach a detection rate above 90%.[17]

Radiologic Findings

Imaging plays an important role in the diagnosis of SARS and monitoring of response to therapy. Depending on the interval between the onset of fever and hospital admission, the initial chest radiography is abnormal in 60-100% percent of cases.[14, 17, 48] The radiographic appearances of SARS share common features with pneumonia of other causes. Progression from a peripheral infiltration or a unilateral focal airspace opacity to unilateral multifocal or bilateral involvement within 1-2 days while disease ongoing is typical finding. Lack of cavitation, lymphadenopathy and pleural effusion are the more distinctive radiographic findings. The most common initial radiographic abnormalities are ground-glass opacifications that do not obscure underlying vessels or focal consolidations of the peripheral, subpleural and lower zones of the lungs.[9, 38, 48] One study reported that the opacities occupy a peripheral or mixed peripheral and axial location in 88% of patients.[48] In a case series, spontaneous pneumomediastinum without preceding positive-pressure ventilation or intubation was observed in 12% of patients and 20% of patients developed evidence of acute respiratory distress syndrome over a period of three weeks.[17] The pleuraldesis-like effect caused by subpleural pneumonic process and the fibrosis and cysts formation cuased by diffuse alveolar damage may associate with the characteristic spontaneous pneumomediastinum in SARS patients. In patients with comorbidities, abnormalities in chest radiography may precede the onset of fever.[39, 40, 44, 48]

High resolution CT is abnormal in 67% of patients with initially normal chest radiographs.[38] The predominant abnormalities found on initial CT scans are areas of sub-pleural focal consolidation with air bronchograms and ground glass opacifications. The lower lobes are predominantly involved, especially in the early stages.[38] In patients at more advanced stages,

there is involvement of the central, perihilar regions by large (>3cm) lesions.[48] Radiologists from the Prince of Wales Hospital, Hong Kong, recommend the following protocol for diagnostic imaging of suspected SARS patients : (1) Patients with symptoms and signs consistent with SARS and with abnormalities on chest radiographs are following up with serial radiography. CT scanning is not required. (2) Patients with symptoms and signs consistent with SARS and with a normal chest radiograph undergo thin-section CT to confirm the diagnosis. They subsequently undergo serial radiography for follow-up.[48]

Clinical Course

The clinical course of SARS is highly variable, ranging from mild symptoms to a severe disease process with respiratory failure and death. Deterioration of clinical condition and progression to respiratory distress syndrome requiring ventilation support and intensive care occurs generally at 7-10 days after symptom onset.[9, 17] SARS may also present with fulminant course, progressing from mild discomfort to respiratory failure requiring mechanical ventilation support within 24 hours.[38-39]

Typical SARS course can be divided into 3 phases :[17]

Phase 1 : viral replication phase, is associated with increasing viral load. Patients presented with clinical symptoms of fever, myalgia and other systemic manifestations generally improved after few days.

Phase 2 : immunopathological damage phase, is characterized by recurrence of fever, oxygen desaturation and radiological progression of pneumonia with falls in viral load. Diarrhea may occur in this phase. Fever recurred in 85% of patients at a mean of 8.9 days. Radiological worsening was noted in 80% at a mean of 7.4 days. IgG seroconversion , correlating with falls in viral load, could be detected from day10 to 15. Severe clinical worsening also occurred in this phase.

Phase 3 : progression into ARDS necessitating ventilation support. 20% of patients progressed to this phase. Concomitant nosocomial sepsis, end-organ damage and severe lymphopenia could be developed in this phase.

In general, 32% of patients required intensive care at a mean of 11 days. Progressive decrease in rates of viral shedding from nasophryngeal secretion, stool, and urine was observed by day 10-21 after symptom onset.[9, 14, 17]

Case Definition

WHO case definition[49] was as follows:

A suspected case was defined by WHO as a person presenting after 1 November 2002 with:

1. Fever > 38 ℃, and
2. Cough, difficulty breathing, or shortness of breath, and
3. Either close contact with a person who is a suspected or probable case of SARS and/or history of travel or residence in an area with recent local transmission of SARS within 10 days of symptom onset.

A probable case is defined as :

1. A suspected case with radiographic findings of pneumonia or acute respiratory syndrome, or
2. A suspected case positive for SARS CoV in one or more laboratory assays, or
3. A suspected case with necropsy evidence of acute respiratory distress syndrome with unknown cause.
4. Exclusion criteria : a case should be ex-

cluded if an alternative diagnosis can fully explain their illness.

The WHO case definitions for suspected SARS have a low sensitivity of 26% and a negative predictive value of 85% for detecting SARS in patients who have not been admitted to hospital.50 The WHO has revised the case definitions in the post-outbreak period with inclusion of radiographic and laboratory findings. (Table2)

Treatment

Because of limited understanding of the pathogenesis and clinical course of this newly emerged disease, treatment strategies for SARS were first developed on theoretical bases and from clinical observation and inferences during the outbreak in 2003. The mainstream therapeutic interventions for SARS involve broad-spectrum antibiotics, antiviral agent, immunomodulatory therapy and supportive care.

A retrospective multicenter study has shown that compared with a matched cohort who received standard treatment, the addition of lopinavir-ritonavir as an initial treatment combined with ribavarin and corticosteroid for SARS was associated with a reduction in the overall death rate (15.6% vs 2.3%) and intubation rate (11% vs 0%).[51-52] Ribavarin was widely chosen as an empirical therapy for SARS because of its broad-spectrum antiviral activity

Table 2. Laboratory confirmation for coronavirus

Recommendation from WHO for laboratory confirmation of SARS infection

- Nucleic acid tests

Reverse transcription polymerase chain reaction (RT-PCR), positive for SARS-CoV using a
validated method from:
1. At least two different clinical specimens (e.g. nasopharyngeal and stool)
OR
2. The same clinical specimen collected on two or more occasions during the course of
the illness (e.g. sequential nasopharyngeal aspirates)
OR
3. Two different assays or repeat RT-PCR using a new RNA extract from the original clinical sample on each occasion of testing.

Seroconversion by ELISA or IFA

• Negative antibody test on acute sate serum followed by positive antibody test on convalescent phase serum tested in parallel.
OR
• Fourfold or greater rise in antibody titre between acute and convalescent phase sera tested in parallel.

- Virus isolation

Isolation in cell culture from any clinical specimen and identification of SARS-CoV using a validated method such as RT-PCR.

WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS) : Updated recommendations October 2004. 2004:11-12

against many DNA and RNA virus. It was commonly used with corticosteroids.[5, 10, 32, 28, 53, 54] The use of ribavarin has attracted a lot of criticism due to its unproven efficacy and more significant toxicity, including hemolysis (76%), decrease in hemoglobin of 20g/l (49%), raised transaminases (40%) and bradycardia (14%).[14, 17] The prevalence of side effects from ribavarin is dose-related.[53] Side effects have also been observed more frequently in the elderly.[55] Oseltamivir phosphate is a neuraminidase inhibitor for the treatment for influenza virus. It was commonly prescribed together with other forms of therapy to SARS patients in some Chinese centers.[5, 8, 53-54] Since there is no evidence that this drug has any efficacy against SARS CoV, it is generally not a recommended treatment except when used as an empirical therapy to cover possible influenza virus infection.[53-54]

Interferons are a family of cytokines important in the cellular immume response. In an uncontrolled study in Toronto, use of interferon alfacon-1 and corticosteroid for SARS patients were associated with reduced disease related oxygen desaturation, more rapid resolution of radiographic lung opacities, and lower levels of creatine kinase.[56] In vitro study of interferons against SARS CoV was carried out in Germany. Interferon beta was found to be more potent than interferon alfa or gamma, and remained effective after viral infection.[57] Theses results suggests that interferon beta is promising.

Human gamma immunoglobulins were used in some hospitals in China and Hong Kong without definite benefit. Convalescent plasma collected from recovered patients was also an experimental treatment used in Hong Kong.[5, 32, 53, 54] Due to the uncertainty effect and conflicting clinical data, its use required more evaluation.

During phase 2 of SARS, the pneumonia and hypoxemia progress despite a fall in the viral load as IgG seroconversion took place. Tissue injury in this phase is assumed due to immunopathology. High dose steroid have been given to prevent immune response mediated injury. Timely use of steroid often led to early improvement in terms of subsidence of fever, resolution of radiographic infiltrates and better oxygenation, as described in many Chinese and Hong Kong reports.[5, 9, 32, 53, 54] There was comparative studies showing the efficacy and safety of pulsed methylprednisolone as an initial therapy compared with a lower dose rigimen.[58] However, pulsed methylprednisolone was identified as a major independent predictor for mortality in one study.[59] The inconsistency of treatment outcomes in SARS could be related to differences in the timing, dosage and duration of corticosteroid use. The ultimate aim should theoretically be to strike an optimal immune balance at the right time so that the patient can mount a sufficient adaptive immune response to eradicate the virus, but without sequelae of irreversible lung damage from immune storm. A protocol was published to have satisfactory clinical outcomes.[53]

Non-invasive positive pressure ventilation (NPPV) has been used with success in SARS patients with respiratory failure.[5, 53] However, NPPV should be carried out only if there is adequate protection for healthcare worker due to high risk of viral transmission and spreading of contaminated aerosol via mask leakage.

Despite treatment efforts, some SARS patient still develop hypoxemic respiratory failure requiring intubation and intensive care. The

actual endotracheal intubation procedures bear a high infective risk and healthcare workers must strictly adhere to all infection control measures. To minimize the risk, the procedure is best performed by highly skilled personnel using rapid sequence intubation.[60] Most centers used ventilation settings according to the strategies for acute respirator distress syndrome. The tidal volume should be kept low at 5-6 ml/kg, plateau pressure be kept less then 30 cm H_2O, and positive end-expiratory pressure (PEEP) be titrate to as low as possible to maintain the oxygenation. Mechanically ventilated patients should be adequately sedated and a short-term neuromuscular blockade may be required.[61]

Furious efforts are being made to determine the optimal treatment regimen and to develop therapeutic agents and vaccines. Nonetheless, despite theses techonological achievements, we remain as vulnerable to this new agent as our ancestors were to previous plaques.

Prevention

In the absence of a vaccine, the most effective way to control a new viral disease such as SARS is to break the chain of transmission. In almost all documented cases, SARS is spread through close face-to-face contact with infected droplets. Three activities: case detection, patient isolation and contact tracing can reduce the number of people exposed to each infectious case and eventually break the chain of transmission.[62] According to WHO recommendation, the three steps should be performed as follow:

1. Case detection aims to identify SARS cases as soon after the onset of illness as possible.
2. Once cases are identified, the next step is to ensure their prompt isolation in a properly equipped facility, and management according to strict infection control procedures.
3. Contact tracing involved the identification of all close contacts of each case and assurance of their careful follow-up, including daily health checks and possible home or facility isolation.

The primary focus of SARS surveillance activities in countries without or with few SARS cases is on the early identification and isolation of patient who have suspected SARS. In contrast, countries which are affected by a severe SARS outbreak must immediately take a variety of measures to contain the epidemic.[63] These measures include:

1. Creation of an emergency operating center
2. Designation of SARS hospitals
3. Institutions of efficient quarantine measures based on specific criteria

In Taiwan, the Department of Health efforts focused on limiting nosocomial transmission by designating SARS hospitals. Fever screen centers were also established to identify potential SARS patient and to minimize the risk of transmission via hospital settings. Patient care capacity was expanded by the construction of additional negative pressure isolation rooms. Quarantine and isolation measures were performed via military facilities, campsites, and home isolation.[64]

Quarantine

Tests to identify SARS patients at the earliest stages of disease are not expected to be widely available soon. Early introduction of quaran-

tine procedures for SARS should therefore be considered by health authorities. Isolation and quarantine procedures will be less effective as more cases accrue. Therefore, stringent measures implemented early in the course of the epidemic prevent the need for stricter measures as the epidemic spreads.[30] Quarantine does not always confine to a hospital or military camp. If patients are not sick enough to warrant admission, the community may be best served by sending such patients home, provided patients can restrict their activities in a responsible manner until they are asymptomatic.[65]

Infection Control in Hospital Setting

Hospital workers remain on the front lines in the global response to SARS. They are at considerable risk of contracting SARS when there is an opportunity for unprotected exposure. In order to protect healthcare workers and to prevent disease dissemination, strict infection control measures and public education are essential.[660]

Droplet infection seems to be the primary route of spread for the SARS virus in the healthcare settings.[20] Recommended measures for droplet-related infection are listed as follow:[66]

1. Patients should wear N-95 masks once symptoms developed and be placed immediately in isolation facilities with negative pressure.
2. Healthcare workers should wear similar masks together with head cover, goggles, gowns, and gloves when caring for these patients.
3. Daily and terminal disinfection should be thorough, with careful washing and disinfection of the bed, handrails, bedside tables, floor, and equipment with hypochlorite solution (1000 ppm).
4. For intubated patients, the use of a closed suction system is essential to avoid air leakage and enhanced disease transmission.

Other recommended measures for infection control include hand washing, theater caps, proper order in getting undressed, avoidance of nebulizer medications, and make use of RSI when intubating SARS patients.[60,66]

The most important lesions learned to date is the decisive power of high-level political commitment: isolation, contact tracing and follow-up, quarantine, and travel restrictions, to contain an outbreak even when sophisticated control tools are lacking. Other successful measures include the design of SARS-dedicated hospitals and fever clinics to minimize the risk of spreading via healthcare settings, mass media campaigns to educate the public and encourage prompt reporting of symptoms, and fever checks at airports and other border points.[67]

The key steps to breaking the chain of transmission are prompt detection and isolation of new sources of infection. At emergency department or other primary care settings, rapid development of clinical decision rules is the essential step in response to such a natural terrorism.[68]

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