

# Update on Severe Acute Respiratory Syndrome (SARS)

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## INTRODUCTION

Severe acute respiratory syndrome (SARS) is a new respiratory infection in humans that was first recognised in Hanoi, Vietnam, in February 2003 [1]. Carlos Urbani, a now-deceased SARS victim himself, was working in Hanoi when he alerted the World Health Organisation (WHO) about this new clinical entity. On 12 March 2003, the WHO issued a global health alert on the disease, then known as atypical pneumonia. The organism has been isolated and identified as a novel coronavirus [2]. It has been proposed that the new virus be named the Urbani SARS-associated coronavirus (SARS-CoV), in honour of the Italian WHO physician and infectious

disease specialist whose initial work in Hanoi led to his untimely demise [3,4]. Besides the reporting blitz by the world media, the speed at which major journals were able to electronically process and release vital scientific information about SARS ensured that it was made readily and extensively available to healthcare workers and the public [5]. Although the Asian-Oceanian Textbook of Radiology was already in press at the time of the SARS outbreak, the editors have recognised the global importance of this Asian-origin disease, and decided to commission this Appendix at very short notice.

## CASE DEFINITION

There are currently two case definitions used in making the clinical diagnosis of SARS, i.e. defini-

tions from WHO and the United States Centers for Disease Control and Prevention (CDC). WHO has two definitions for suspect cases and three definitions for probable cases of SARS. The first definition of a suspect case is a person presenting after 1 November 2002 with a history of: (1) high fever (exceeding 38°C); (2) cough or breathing difficulty; and (3) one or more of the following exposures during the 10 days prior to onset of symptoms: close contact with a person who is a suspect 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. The second WHO definition of a suspect case is 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 exposures listed in the first definition [6]. The three WHO definitions of a probable case of SARS are: (1) a suspect case with radiographical evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest radiographs; (2) a suspect case of SARS that is positive for SARS coronavirus by one or more assays; and (3) a suspect case with autopsy findings consistent with the pathology of RDS without an identifiable cause. WHO emphasises that as SARS is currently a diagnosis of exclusion, the status of a reported case may change with time. The initial classification may also be discarded if an alternative diagnosis can fully explain a patient's illness [6].

The CDC also classifies cases into two categories, depending on a combination of clinical, epidemiological and laboratory criteria. A probable case is one that meets clinical criteria for severe respiratory illness of unknown aetiology and epidemiological criteria for exposure; with laboratory criteria confirmed or undetermined. A suspect case is one that meets the clinical criteria for moderate respiratory illness of unknown aetiology and epidemiological criteria for exposure; with laboratory criteria

confirmed or undetermined [7]. Clinical criteria of moderate respiratory illness consists of (1) temperature greater than 38°C, and (2) one or more clinical findings of respiratory illness (e.g. cough, shortness of breath, difficulty breathing, or hypoxia). Clinical criteria of severe respiratory illness are similar to those for moderate illness with inclusion of the additional criterion of radiographical evidence of pneumonia, or respiratory distress syndrome, or autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause [7]. CDC epidemiological criteria consist of (1) 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 (2) close contact within 10 days of onset of symptoms with a person suspected of having SARS [7]. Confirmed laboratory criteria are (1) detection of antibody to SARS-associated coronavirus (SARS-CoV) in a serum sample, (2) detection of SARS-CoV by reverse transcription polymerase chain reaction (RT-PCR) confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers, or (3) isolation of SARS-CoV [7].

Rainer et al, in a prospective observational study, found that the current WHO guidelines for diagnosing suspected SARS may not be sufficiently sensitive in assessing patients before admission to hospital. They found that in the early stages of SARS, the main discriminating symptoms are not cough and breathing difficulty but fever, chills, myalgia, rigors and possibly, abdominal pain and headache. Radiographical evidence of pneumonic changes have also been found to often precede fever, with documented fever being uncommon in the early stages. Daily follow-up, evaluation of non-respiratory systemic symptoms, and chest radiography have been suggested as better screening tools [8]. As data about SARS is being constantly reviewed and updated, healthcare workers are

advised to refer to the various websites, particularly those of WHO and CDC, for the latest information [6,7].

## VIROLOGY AND EPIDEMIOLOGY

Coronaviruses cause up to 30% of cases of the “common cold” but they rarely cause lower respiratory tract infections [9]. Coronavirus are a family of positive stranded RNA viruses that normally infect humans, cattle, birds and pigs [10]. This virus may have mutated from its parent virus that causes severe epizootics in poultry [9]. It is thought that the SARS is most likely a zoonosis, i.e. a disease transmitted from animals to humans, and that the virus was transmitted to humans by close contact with animals, particularly water fowl such as ducks. The genome of the SARS virus has been established. Two distinct genotypes are present and can be traced to the origins of the initial infections [10]. Sequencing the genome is important for the design of new and precise molecular probes in diagnostic tests, and for studying the life cycle of the virus and drugs to combat it [11].

The epidemic started in Guangdong province of China in November 2002 and since then, has spread worldwide with a total of 8437 reported probable cases as of 11 July 2003 [12]. A seafood dealer who was warded in the Zhongshan No. 3 hospital in early February 2003 is widely believed to be the first super-spreader of the SARS virus. He infected 90 people, including one of his doctors who subsequently travelled to Hong Kong and stayed at the Metropole hotel. This doctor infected among others, seven guests staying on the same floor of the hotel. Besides seeding the infection in Hong Kong, these guests then transmitted the disease to Hanoi, Singapore and Toronto, Canada, starting the world epidemic [13]. Epidemiological data suggests that the virus is spread by airborne respiratory droplets or by direct contact. The largest number of patients have been recorded in China (5327 cases, 348

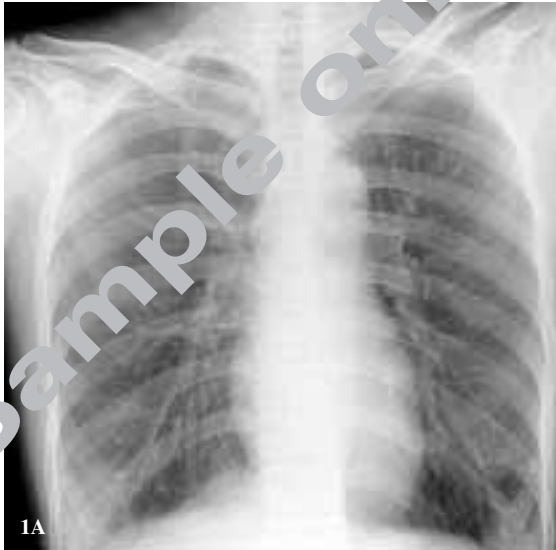
deaths), Hong Kong (1755 cases, 298 deaths), Taiwan (671 cases, 84 deaths), Canada (250 cases, 38 deaths), and Singapore (206 cases, 32 deaths) [12].

## DIAGNOSTIC EVALUATION

Initial diagnostic tests recommended by the CDC in the evaluation of suspected SARS patients consist of chest radiographs, pulse oximetry, blood cultures, sputum Gram stain and culture, and testing for viral respiratory pathogens, particularly influenza A and B and respiratory syncytial virus. All available respiratory, blood and serum specimens should be saved until a specific diagnosis is made. Besides specific instructions for collection of specimens, medical staff evaluating suspected SARS cases should employ standard precautions, including airborne and contact precautions [14]. Currently, an international network of 11 laboratories in 9 countries are working to produce a definitive test to assist in the diagnosis of SARS patients [11].

## CLINICAL FEATURES

The incubation period ranges from 2 to 16 days, with a mean of six days. An incubation period of 10 days has been adopted by WHO and CDC [6,7]. Patients diagnosed with SARS commonly present with flu-like symptoms consisting of a rapid onset of high fever, malaise, chills, headache, and body ache. Other symptoms include cough and dyspnoea. [2,8,15-18]. Upper respiratory tract symptoms are uncommon, occurring in only 25% of patients, while diarrhoea occurs in 10% of patients. The illness follows a variable clinical course. Patient outcome is strongly associated with the patient's age, with mortality rapidly increasing in the older patient [16-18]. The overall mortality rate is approximately 15% [16]. There is often a profound neutropenia, lymphopenia, thrombocytopenia and altered liver function tests in these patients, in keeping with a severe systemic viral infection.



*Fig. 1: Young female healthcare worker who presented with fever. Type 1 radiographical pattern. (A) Chest radiograph taken on day 5 from the start of symptoms shows ill-defined areas of air-space shadowing at the periphery of both lower zones. (B) Chest radiograph taken on day 12 shows increase in air-space shadowing at both lower zones with the air-bronchogram effect at the right lower zone. (C) Chest radiograph taken at discharge (day 18) shows improvement with small residual areas of air-space shadowing.*

macrophages have an important role in the pathogenesis of SARS [19]. An interesting observation from autopsies in Singapore is the finding of significant thromboembolism in peripheral veins and the pulmonary vasculature [11].

### IMAGING FINDINGS

Imaging has an important role in the diagnosis and management of patients infected by SARS. Both chest radiography and high-resolution computed tomography (HRCT) are routinely used for evaluation of this disease. Chest radiographical findings are used as part of the case definition [6,7], and are considered an important component of clinical management by both WHO and CDC. Imaging also has a role in monitoring disease progression during treatment. An imaging protocol for patients with clinical features of SARS has been recommended [20]. Patients who have symptoms and signs consistent with SARS and abnormalities

### PATHOLOGICAL FEATURES

Pathologically, there is a spectrum of findings in the lung, from diffuse alveolar damage to epithelial cell proliferation and macrophage infiltration [19]. The alveolar cells are initially severely injured. With healing, there is proliferation of type II pneumocytes. Unlike other causes of diffuse alveolar cell injury where neutrophils and fibroblasts are present, in alveolar wall injury of SARS, there is a predominance of macrophages. This infiltration by macrophages in the lung suggests that pro-inflammatory cytokines released by



*Fig. 2: Middle-aged woman who presented with fever. Type 4 radiographical pattern. (A) Chest radiograph taken on day 7 from the start of symptoms shows an area of ill-defined ground-glass opacity at the right lower zone. (B) Chest radiograph taken on day 10 shows rapid progression with patchy areas of consolidation and ground-glass opacity involving all zones of both lungs. (C) Chest radiograph taken on day 15 shows extensive and diffuse air-space shadowing in both lungs consistent with acute respiratory distress syndrome. The patient died 11 days later.*

found on chest radiographs are followed-up serially with radiographs. Patients who have symptoms and signs consistent with SARS but with normal chest radiographs undergo HRCT to confirm the diagnosis, and have serial radiography for follow-up. Patients who have minor symptoms and signs that do not fulfil the definition of SARS do not undergo HRCT [20].

### **Radiography**

Chest radiographs demonstrate a spectrum of findings ranging from focal segmental air space opacification to extensive rapidly developing pul-

monary opacification [15,21]. At presentation, most patients have an area of air-space consolidation on chest radiographs [15,17,22]. The peripheral location of air-space opacification is a common radiographical feature of SARS, occurring in 75% of cases [23]. The lower zones and the right lung are more frequently involved [23]. For most patients, deterioration is shown on radiographs as multifocal unilateral or bilateral opacification [15,17,23]. The finding of confluent consolidation is similar to that of acute respiratory distress syndrome and indicates a grave prognosis [20]. The radiographical appearances of peripheral air-space opacities in SARS is however indistinguishable from other causes of atypical pneumonia, such as *Mycoplasma*, *Chlamydia* and *Legionella* [23].

Four patterns of progressive radiographical findings have been described. In type 1, the radiographical appearances deteriorate for a week followed by improvement (Fig. 1). In type 2, the

appearance fluctuates with at least one intervening period of significant improvement, followed by deterioration and later recovery. In type 3, the appearance remains relatively static for 10 days followed by improvement. Type 4 involves progressive deterioration leading to death [23] (Fig. 2). Relevant negative findings on chest radiographs include absence of cavitation, calcification, reticular or nodular pattern of opacification, lymphadenopathy, or pleural effusion [23].

### Computed tomography

CT of the lungs demonstrate focal peripheral air space opacification with regions of normal intervening lung that can progress to diffuse air space opacification or ground-glass appearance, similar to findings in acute respiratory distress syndrome [21]. If the patient with suspected SARS has a normal chest radiograph and in the absence of lymphadenopathy or pleural abnormalities, HRCT of the lungs is recommended [20]. The lower lobes of the lungs are preferentially affected [24]. In more severe cases, lesions involve the upper lobes or become bilateral. Lesions usually begin at the lung periphery but may progress to the central or perihilar regions [24].

On HRCT, lesions are seen as areas of ground-glass opacification, consolidation, or a mixture of both (Fig. 3). Thickening of the intralobular interstitium or interlobar septa may be present. Marked septal thickening may produce a “crazy paving” appearance. None of these HRCT findings are however specific. HRCT findings may precede those seen on radiographs by 2 days. HRCT is also useful for detecting paraspinal lung lesions that may be difficult to detect on chest radiographs [24]. A geographical pattern of ground-glass attenuation has also been described [22]. HRCT is useful for detection of pulmonary fibrosis that may develop early in patients with SARS. Patients who are older and have more severe disease are more likely to develop pulmonary fibrosis [25].



Fig. 3: Young man who presented with fever and cough. Axial HRCT scan shows patchy foci of ground-glass opacity and consolidation predominantly at the periphery of the right upper and lower lobes. Small areas of ground-glass opacity are also seen at the periphery of the left lower lobe.

### TREATMENT

Currently, there is no known treatment that is effective for the new coronavirus. Therapy is supportive, with use of mechanical ventilation to improve oxygenation and to decrease the work of breathing. A lung-protective strategy has been suggested [18]. Ribavirin (an antiviral drug) and corticosteroids have been used to treat SARS [15-17]. Others have proposed empirical treatment with corticosteroids, broad spectrum antiviral agent, and antibacterial cover [18,26]. Presently, the efficacy of these drugs appears to be largely anecdotal and have been questioned [27-29].

### RADIOLOGY DEPARTMENT FUNCTIONS

Radiology departments have an important role in hospitals managing confirmed or potential SARS patients. Besides diagnosis and monitoring of affected patients, there is a responsibility to ensure that other non-SARS patients and staff are not put at risk. The experiences of two large hospitals at the frontline of battling SARS, the Prince of Wales Hospital in Hong Kong and Tan Tock Seng Hospital in Singapore, have been described in recent articles [30-32].

Two imaging protocols have been proposed for patients clinically suspected and confirmed to have

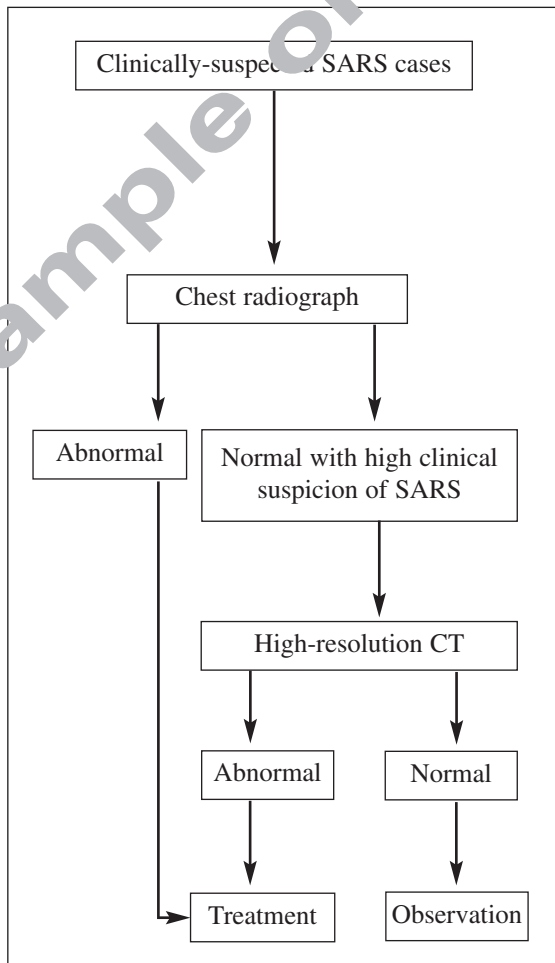


Fig. 4: Flow diagram shows imaging protocol for patients suspected of having SARS [30].

SARS, taking into consideration factors such as availability of imaging resources, number of patients involved, radiation hazards and sensitivity of imaging tests [30] (Figs. 4 & 5). Similar to measures adopted by the hospital, it has been recommended that the radiology department also be stratified into areas according to the levels of risk of SARS. All examination rooms are classified as ultrahigh-risk areas for the time when patients positive or suspected for having SARS are being examined. Appropriate infection control measures against SARS are adopted at ultrahigh-risk, high-risk, and moderate-risk areas, and are defined, distributed and strictly followed by all departmental

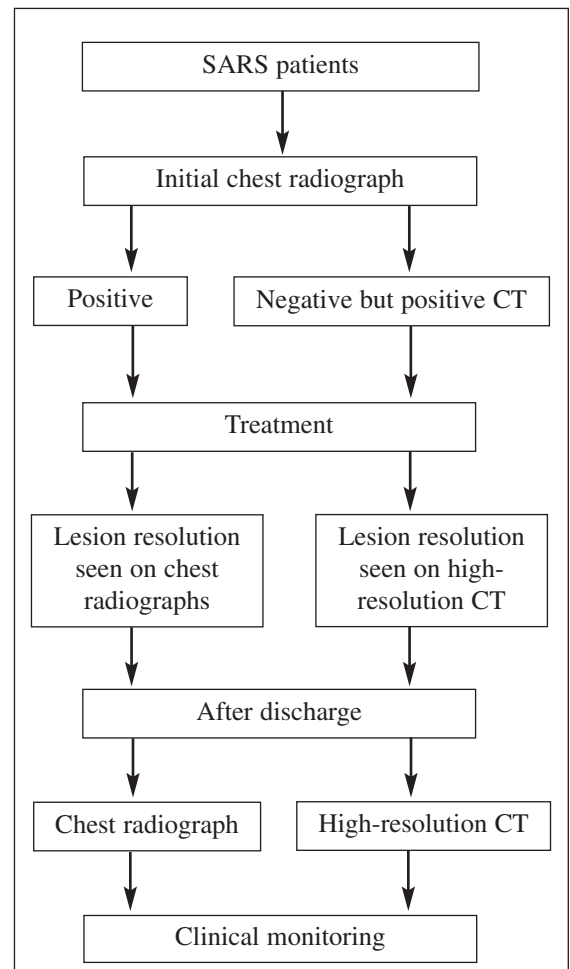


Fig. 5: Flow diagram shows imaging protocol for patients with SARS [30]. Disease progression or resolution of SARS is better seen on CT for retrocardiac, paraspinal or posterior costophrenic angle pulmonary abnormalities.

staff. The establishment of a dedicated website has also been found to be useful in disseminating timely information about the disease to a global audience [30].

During a SARS outbreak, the radiology department should be reorganised in order to reach its goal of reducing the risk of cross-infection between patients as well as reducing the risk of infection to staff. Close involvement of the hospital infection control team is important. A policy of physically segregating inpatients without suspected or confirmed SARS from other groups has been advocat-

ed. The reasons are that these inpatients may have a provisional diagnosis of a non-SARS-related disease that causes symptoms in common with SARS and may in addition, are at risk of cross-infection. Physical segregation may be achieved using location or time. In practice, the patient's clinical condition often dictates the timing of the examination. Wherever possible, facilities for imaging patients with SARS should be located outside the main department, e.g. portable radiography and ultrasonography units used in intensive care and in the general wards. A portable CT scanner, if available, should be placed in a suitable location for the imaging of all probable SARS patients or cases in which SARS is highly suspected [31,32].

All staff in the department must be taught the use of personal protective equipment, and to observe universal precautions in dealing with patients with SARS or in whom the SARS status is unknown [32]. Close health monitoring is essential in ensuring early detection of possible SARS infection of a staff member. One simple method is thrice daily temperature monitoring. Those with a temperature higher than 37.5°C will be sent to the emergency department for screening, and given medical leave or isolated as deemed necessary [32]. A departmental infection control team should be formed to produce, continually update and enforce guidelines, and to educate staff. Various procedures, e.g. allocating appointments, preparing the patient, examining the patient, and protocols for each specific modality need to be designed and disseminated [31,32].

## CONCLUSION

SARS is a highly contagious and lethal viral infection that has since its recent emergence, left an extensive and deep worldwide imprint. Over a brief period of weeks, much about the disease has been discovered through international scientific and med-

ical collaboration and cooperation, including identification of its genetic code, mainly out of necessity and self-preservation. At the time of writing this Appendix, WHO has declared the SARS outbreak over. There remains much to be done with respect to detection, diagnosis and treatment, as well as maintenance of vigilance and public health measures. Although imaging has an important role in assessment of patients suspected to have SARS, radiographical and CT findings have been found to be non-specific at present, and interpretation in conjunction with sufficient clinical information is required.

## REFERENCES

1. Acute respiratory syndrome. China, Hong Kong Special Administrative Region of China, and Viet Nam. *Wkly Epidemiol Rec* 2003;78:73-74.
2. Peiris JSM, Lai ST, Poon LLM, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003;361:1319-1325.
3. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus in patients with acute respiratory syndrome. *N Engl J Med* 2003;348:1953-1966.
4. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003;348:1967-1976.
5. Drazien JM, Campion EW. SARS, the internet, and the journal. *N Engl J Med* 2003;348:2029.
6. World Health Organization. Case definitions for surveillance of severe acute respiratory syndrome (SARS). <http://www.who.int/csr/casedefinition/en/> Updated 1 May 2003 (accessed 21 July 2003)
7. Centers for Disease Control and Prevention. Updated interim U.S. case definition for severe acute respiratory syndrome (SARS). <http://www.cdc.gov/ncidod/sars/casedefinition> Updated 17 July 2003 (accessed 21 July 2003)
8. Rainer TH, Cameron PA, Smit D, et al. Evaluation of WHO criteria for identifying patients with severe acute respiratory syndrome out of hospital: prospective observational study. *Br Med J* 2003;326:1354-1358.
9. Holmes KV. SARS-corona virus. *N Engl J Med* 2003;348:1948-1951.
10. Ruan Y, Chia LW, Ling AE, et al. Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection. *Lancet* 2003;361:1779-1790.
11. Chee YC. Severe acute respiratory syndrome (SARS) - 150 days on. *Ann Acad Med Singapore* 2003;32:277-280.
12. World Health Organization. Cumulative number of reported probable cases of SARS from 1 November 2002 to 11 July 2003. [http://www.who.int/csr/sars/country/2003\\_07\\_11](http://www.who.int/csr/sars/country/2003_07_11) (accessed 21 July 2003)

13. Forney M. Stalking a killer. *Time* 21 April 2003:46-48.
14. Centers for Disease Control and Prevention. Diagnosis/evaluation of severe acute respiratory syndrome (SARS). <http://www.cdc.gov/ncidod/sars/diagnosis> Updated 11 July 2003 (accessed 21 July 2003)
15. Lee N, Peiris J, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;348:1986-1994.
16. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003;361:1767-1773.
17. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Kong Kong. *N Engl J Med* 2003;348:1977-1985.
18. Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. *N Engl J Med* 2003;348:1995-2005.
19. Nicholls JM, Poon LLM, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003;361:1773-1778.
20. Antonio GE, Wong KT, Hui DSC, et al. Imaging of severe acute respiratory syndrome in Hong Kong. *Am J Roentgenol* 2003;181:11-17.
21. Nicolaou S, Al-Nakshabandi NA, Müller NL. SARS: imaging of severe acute respiratory syndrome. *Am J Roentgenol* 2003;180:1247-1249.
22. Müller NL, Ooi GC, Khong PL, Nicolaou S. Severe acute respiratory syndrome: radiographic and CT findings. *Am J Roentgenol* 2003;181:3-8.
23. Wong KT, Antonio GE, Hui DSC, et al. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 patients. *Radiology* 2003;228: in press. (20 May 2003- Epub ahead of print)
24. Wong KT, Antonio GE, Hui DSC, et al. Thin-section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. *Radiology* 2003;228: in press. (8 May 2003- Epub ahead of print)
25. Antonio GE, Wong KT, Hui DSC, et al. Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. *Radiology* 2003;228: in press. (12 June 2003- Epub ahead of print)
26. Chan-Yeung M, Yu WC. Outbreak of severe acute respiratory syndrome in Hong Kong Special Administrative Region: case report. *Br Med J* 2003;326:850-852.
27. Hsu LY, Lee CC, Green JA, et al. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis* 2003;9:713-717.
28. Oba Y. The use of corticosteroids in SARS. *N Engl J Med* 2003;348:2034-2035.
29. World Health Organization. Management of severe acute respiratory syndrome (SARS). <http://www.who.int/csr/sars/management/en/> Updated 11 April 2003 (accessed 21 July 2003).
30. Ho SSY, Chan PL, Wong PK, et al. Eye of the storm: the roles of a radiology department in the outbreak of severe acute respiratory syndrome. *Am J Roentgenol* 2003;181:19-24.
31. King AD, Ching ASC, Chan PL, et al. Severe acute respiratory syndrome: avoiding the spread of infection in a radiology department. *Am J Roentgenol* 2003;181:25-27.
32. Tsou IYY, Goh JSK, Kaw GJL, Chee TSG. Severe acute respiratory syndrome: management and reconfiguration of a radiology department in an infectious disease situation. *Radiology* 2003; 229: in press. (9 July 2003 - Epub ahead of print)