Severe Acute Respiratory Syndrome

Chapter 1 - Clinical Review for IDCNA
Emerging and Re-Emerging Infectious Diseases

Title:
Severe Acute Respiratory Syndrome (SARS) – Historical, Epidemiological, and Clinical features
Running Head: Severe Acute Respiratory Syndrome (SARS)

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Key Points:

- Severe acute respiratory syndrome (SARS) is a highly infectious respiratory disease with significant morbidity and mortality.
- SARS is a zoonosis caused by SARS-coronavirus (SARS-CoV), which first emerged in China and gained global notoriety in 2002-2003 causing a travel-related global outbreak with 8,098 cases and 774 deaths. Nosocomial transmission of SARS-CoV was common.
- The main mode of transmission of SARS-CoV is person-to-person spread through inhalation of respiratory droplets. Faeco-oral transmission via contaminated fomite on surfaces has been recorded.
- The specific animal host reservoir remains unknown. Horseshoe bats are a natural reservoir of coronaviruses that are distantly related to SARS-CoV and the threat of global spread is ever present.
- Fever and respiratory symptoms like influenza predominate and diarrhea is common. About 25% of cases can rapidly progress and require intensive care.
- Treatment involves supportive care with appropriate fluid and electrolyte balance, oxygenation, and organ support. Convalescent plasma, protease inhibitors, and interferon might confer beneficial effects based on retrospective analyses whereas ribavirin led to significant haemolysis while systemic corticosteroids might prolong viral shedding.
- Prevention requires strict infection control procedures with respiratory and contact precautions for routine care but upgrade to airborne precaution is needed for managing aerosol-generating procedures. There are no SARS-CoV specific vaccines.
Abstract

In November 2002, a novel β coronavirus, the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), emerged as a lethal zoonotic human pathogen from China and rapidly spread worldwide. It first emerged as “atypical pneumonia” in Foshan city, China where many healthcare workers were infected by person-to-person respiratory or contact spread. SARS-CoV subsequently rapidly spread globally through travel related person-to-person spread. Over 8,098 people fell ill with SARS and 774 died before the epidemic ended in July 2003. No cases of SARS have been reported after 2004. The host reservoir of SARS-CoV remains unknown. SARS-like CoVs have been detected in horseshoe bats, suggesting bats as the reservoir, while civet cats served as the intermediary source of transmission to humans in 2002-2003. The main mode of transmission of SARS-CoV is through inhalation of respiratory droplets. Faeco-oral transmission via contaminated fomite on surfaces has been recorded. Manual ventilation before intubation, tracheal intubation, non-invasive ventilation, and tracheotomy were identified as the respiratory procedures that increased the risk of nosocomial SARS-CoV transmission to healthcare workers. Strict infection control procedures with respiratory and contact precautions are key to prevention of spread but airborne precaution is needed for aerosol-generating procedures. Fever and respiratory symptoms predominate, and diarrhea is common. Treatment involves supportive care with appropriate fluid and electrolyte balance, oxygenation, and organ support. There are no specific antiviral treatments available. Convalescent plasma, protease inhibitors, and interferon might confer beneficial effects. Ribavirin causes haemolysis and systemic corticosteroids can prolong viral shedding. There are no SARS-CoV specific vaccines.
Introduction

Over the past two decades two previously unknown coronaviruses, the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) have focused medical, scientific and media attention due to their lethal nature and epidemic potential. In November 2002, the first case of severe acute respiratory syndrome (SARS) occurred in Foshan, China, and in June 2012, the first case of MERS died at a hospital in Jeddah, Saudi Arabia. Both zoonotic diseases remain on the WHO list of blue print priority diseases since they remain global threats to global public health security. This review focuses on the historical, epidemiological and clinical features of SARS.

Historical

Before 2003, only two coronaviruses, human coronavirus 229E (HCoV-229E) and HCoV-OC43, were known to cause human disease. These manifest with mild symptoms like the common cold in adults and with more severe disease in infants, the elderly and the immunosuppressed. In November 2002, unusual cases of ‘atypical pneumonia’ of unknown aetiology occurred in Foshan city in Guangdong province in China where many healthcare workers became infected. The infection was brought to Hong Kong on 21st Feb 2003 by a physician who had looked after similar cases of atypical pneumonia in mainland China, leading to subsequent outbreaks of severe pneumonia in Hong Kong labeled by the WHO as “Severe acute respiratory syndrome” (SARS) on 15th March 2003. Several months elapsed and several hundred cases of SARS were observed before SARS-CoV was identified. A novel β coronavirus (SARS-CoV) of lineage B was confirmed as the cause of the atypical pneumonia cases on 22 March 2003. The SARS-CoV epidemic spread to 29 countries and regions, and it was evident that the global public health, medical and scientific communities were not adequately prepared for the emergence of SARS. Chains of human-to-human transmission occurred in Toronto in Canada, Hong Kong Special Administrative Region of China, Chinese Taipei, Singapore, and Hanoi, Viet Nam. The history of the SARS epidemic was short and WHO declared the end of the SARS epidemic in July, 2003. There
were a total of 8,096 SARS cases (which included 774 deaths)\(^4\) reported from 29 countries and regions. \(^5\) Figure 1 shows the geographical map of distribution of SARS cases.

During the epidemic, SARS caused major disruptions to international air travel, and had a major impact on the health services and businesses in affected countries. \(^6\) Since July 2003, there have been four occasions when SARS has reappeared, three of these were attributed to breaches in laboratory biosafety in Singapore, Taipei and Beijing, where 7 cases were associated with one chain of transmission and with hospital spread. The fourth incident in Guangdong province, China resulted in four sporadic community-acquired cases over a six-week period from Dec 2003 to Jan 2004. Three cases had exposure to animals or environmental sources. There was no further community transmission.

**Virology**

Coronaviruses (CoVs; order *Nidovirales*, family *Coronaviridae*, subfamily *Coronavirinae*) are a group of enveloped, positive-sense, single-stranded, highly diverse RNA viruses that are further divided into four genera: \(\alpha\), \(\beta\), \(\gamma\) and \(\delta\).\(^7\) CoVs may cause diseases of varying severity in different systems in humans and other animal species. In March 2003, a novel group 2b \(\beta\) CoV was confirmed as the causative agent responsible for SARS-CoV infection.\(^4,8,9\) The genome sequence of the SARS-CoV did not bear close relationship to any of the previously identified CoVs.\(^10,11\)

SARS-CoV genome consists of 5′-methylated caps and 3′-polyadenylated tails. The partially overlapping 5′-terminal open reading frame 1a/b (ORF1a/b) is within the 5′ two-thirds of the CoV genome and encodes the large replicase polyprotein 1a (pp1a) and pp1ab. These polyproteins are cleaved by 3C-like serine protease and papain-like cysteine protease to produce non-structural proteins, such as RNA polymerase and helicase, which are important enzymes involved in the transcription and replication of CoVs. The 3′ one-third of the CoV genome encodes the structural proteins [spike(S), envelope (E), membrane (M) and nucleocapsid (N)], which are important for virus–cell-receptor binding and assembly of virion, other accessory proteins and non-structural proteins that may have immunomodulatory effects.\(^7\)
Host Reservoir

Data from a retrospective serology study done in Guangzhou in southern China, suggested that the SARS-CoV might have transmitted from animal species to humans in the wet market, as a high sero-prevalence (16.7%) was found among asymptomatic wild animal salesmen. A highly similar variant of SARS-CoV was detected in palm civets at an animal market located in Shenzhen. Masked palm civets were then assumed to be accountable for the transmission of SARS-CoV to humans as 30% of wild animal handlers were found to have positive serology against SARS-CoV infection compared to 1% of controls in the Guangdong province. Additionally, up to 39% of SARS-CoV cases that arose in the early stage of the outbreak were associated with a history of exposure to animal markets. This assumption was further enhanced by an epidemiology linkage in three of the four patients to indirect or direct contact with palm civets during the sporadic outbreaks of SARS-CoV infection that occurred in Guangzhou in December 2003 and January 2004. However, Chinese horseshoe bats were later found to carry SARS-like CoVs in 2005, with a high degree of nucleotide sequence similarity (88-92%) to human or civet cat isolates, suggesting that bats could well have been the natural source of an early ancestor of SARS-CoV. It remains uncertain as to whether an intermediate mammalian host is involved prior to human transmission.

Pathogenesis

The pathogenesis of SARS is complex, and not fully defined since multiple factors govern the wide ranging clinical manifestations from mild to severe disease. Apart from respiratory tract, SARS-CoV can infect several organs and cell types during the course of the disease including intestinal mucosal cells, renal tubular epithelial cells, neurons and cells of the lymphoid and reticuloendothelial system. Entry into host cells and pathology:

SARS-CoV invades humans through the respiratory tract as the entry site and infection occurs in 3 steps: receptor binding, conformational changes in S glycoprotein, and cathepsin L proteolysis within endosomes. Entry of SARS-CoV is mediated by angiotensin-converting enzyme 2 (ACE2), a metallopeptidase that is expressed on many human organ tissues, as the host functional receptor. ACE2 is present abundantly in the epithelia of
human lungs and small intestine,\textsuperscript{23} but the presence of ACE2 may not be the sole requirement for SARS-CoV tropism. One example is that despite the abundant expression of ACE2 in vascular endothelial cells and intestinal smooth muscle cells, SARS-CoV was not detected in these cells while SARS-CoV was found in colonic enterocytes and hepatocytes without ACE2 expression.\textsuperscript{23,24}

**Histology:**

Several autopsies of SARS patients showed the predominant pathological finding as diffuse alveolar damage (DAD). Lung histopathology in patients with SARS included DAD, loss of cilia, squamous metaplasia, denudation of bronchial epithelia, giant-cell infiltrate, with a marked increase in macrophages in the alveoli and the interstitium. ACE2 may contribute to the development of DAD. SARS-CoV infections and the S glycoprotein of the SARS-CoV could reduce ACE2 expression. In the mice model, injection of SARS-CoV S glycoprotein worsened acute lung injury (ALI) in vivo that could be reduced by blocking the renin-angiotensin pathway.\textsuperscript{25} In addition, over-expression of SARS-CoV proteins such as 3a and 7a proteins, which were expressed in the lungs and intestinal tissues of SARS patients, could induce apoptosis in vitro.\textsuperscript{26,27}

Splenic atrophy of the white pulp, haemophagocytosis, hyaline membranes, and secondary bacterial pneumonia were observed.\textsuperscript{28,29} Lesions resembling cryptogenic organizing pneumonia (COP) in subpleural regions were also seen.\textsuperscript{30} Extensive expression of SARS-CoV antigen in type I pneumocytes in cynomologus macaques experimentally infected with SARS-CoV was noted at day 4, suggesting that type I pneumocytes might be the early primary target for SARS-CoV infection.\textsuperscript{31} Diarrhoea was present in up to 70\% of SARS cases.\textsuperscript{24,32} In specimens obtained by colonoscopy or post-mortem examination, active viral replication was noted within the small and large intestine with minimal architectural disruption. SARS-CoV infection was confirmed by viral culture of these specimens while SARS-CoV RNA was detected in the stool specimens for almost 10 weeks after illness onset.\textsuperscript{24} The presence of diarrhea and mortality were associated with a higher nasopharyngeal SARS-CoV viral load on day 10 after illness onset.\textsuperscript{33}

**Immune responses and immunopathology:**

Whilst innate and acquired immune responses enable containment of virus and mild disease, cytokine dysregulation, viral cytopathic effects, down-regulation of lung ACE 2, abnormal
immune responses and autoimmune mechanisms may lead to more severe disease and death. Disease progression in SARS may be related to activation of T-helper (Th1) cell-mediated immunity and hyperinnate inflammatory response.\cite{28,32} Marked increases in the Th1 and inflammatory cytokines (IFN-\(\gamma\), IL-1, IL-6 and IL-12) were noted for over 2 weeks after illness onset in a study of 20 adults with SARS-CoV infection, together with marked increases in chemokines such as Th1 chemokine IFN-g-inducible protein-10 (IP-10), neutrophil chemokine IL-8, and monocyte chemoattractant protein-1 (MCP-1).\cite{34} In mice infected with SARS-CoV, T cells played an important role in SARS-CoV clearance whereas a reduced T cell response contributed to severe disease.\cite{35} In another study of mice infected with SARS-CoV, robust virus replication accompanied by delayed type I IFN (IFN-I) response was observed orchestrating inflammatory responses and lung immunopathology with reduced survival while early administration of IFN-I ameliorated immunopathology. This delayed IFN-I signaling was thought to promote the accumulation of pathogenic inflammatory monocyte-macrophages (IMMs), leading to elevated lung cytokine/chemokine levels, vascular leakage, and impaired virus-specific T cell responses while genetic ablation of the IFN-\(\alpha\beta\) receptor (IFNAR) or IMM depletion protected mice from fatal infection, without affecting viral load.\cite{36}

In addition, Toll-like receptors (TLR) signaling through the TRIF adaptor protein might play a role in protecting mice from lethal SARS-CoV disease based on a study of the innate responses in mice.\cite{37} TLR3(-/-), TLR4(-/-), and TRIF-related adapted molecule [TRAM](-/-) mice were more prone to SARS-CoV infection than wild-type mice although there was only transient weight loss without mortality. In contrast, mice deficient in the TLR3/TLR4 adaptor TRIF were highly susceptible to SARS-CoV infection, with marked weight loss, more lung pathology, higher viral titers, impaired lung function, and mortality. In TIR-domain-containing adapter-inducing interferon-\(\beta\) [TRIF(-/-)] mice infected with SARS-CoV, distinct changes in inflammation occurred including excess infiltration of neutrophils and inflammatory cells that correlated with increased pathology of other known causes of ARDS. Aberrant proinflammatory cytokines, chemokines, and interferon-stimulated gene (ISG) signaling programs were observed following infection of TRIF(-/-) mice that resembled those seen in human patients with poor clinical outcome following SARS-CoV
infection. These findings suggest the importance of TLR adaptor signaling in generating a balanced protective innate immune response to highly pathogenic CoV infections.\textsuperscript{37} In addition, SARS-CoV M protein may function as a cytosolic pathogen-associated molecular pattern to stimulate IFN-β production by activating a TLR-related TRAF3-independent signaling cascade.\textsuperscript{38}

A case-control study conducted in Chinese patients with SARS-CoV infection and healthy controls has shown that genetic variants of interleukin (IL)-12 receptor B1 (IL12RB1) predispose to SARS-CoV infection.\textsuperscript{39} Another case control study has shown that Mannose-binding lectin (MBL), a key molecule in innate immunity that functions as an ante-antibody before specific antibody response, contributes to the first-line host defense against SARS-CoV and that MBL deficiency is a predisposing factor to SARS-CoV infection.\textsuperscript{40}

In macaques infected with SARS-CoV, there is evidence that anti-spike IgG causes severe ALI by altering macrophage inflammation-resolving response in infected lungs. In acutely infected macaques, there was functional polarization of alveolar macrophages, demonstrating wound-healing and pro-inflammatory characteristics simultaneously. However, the presence of S-IgG before clearance of virus aborted wound-healing responses and promoted production of IL-8 and MCP1 with recruitment of proinflammatory monocytes/macrophages. Interestingly, the sera of patients who had succumbed to SARS-CoV infection enhanced SARS-CoV-induced MCP1 and IL-8 production by human monocyte-derived wound-healing macrophages, whereas blockade of FcγR reduced such effects. The findings reveal a mechanism responsible for virus-mediated ALI and define a pathological consequence of viral specific antibody response, in addition to providing some insight on a potential target for treatment of SARS-CoV.\textsuperscript{41}

**Epidemiology and Disease transmission**

**Discovery and spread**

In a chest hospital in Guangzhou city, a retrospective study of 55 patients hospitalized with “atypical pneumonia” between January 24 and February 18, 2003 showed a positive culture of SARS-CoV in the nasopharyngeal aspirates of 3 patients, and positive serology to SARS-CoV in 48 patients (87%). The genetic sequence of the virus isolated from patients in
Guangdong was found to be prototypical of the SARS-CoV found later in affected areas around the world.\textsuperscript{42}

The index case for the major SARS-CoV outbreak in Hong Kong was a 64-year old male renal physician, who travelled from the Guangdong province on February 21, 2003 to Hong Kong.\textsuperscript{2,4} SARS-CoV was transmitted to at least 16 patrons of Hotel M where he stayed on the 9th floor. The renal physician subsequently died of severe pneumonia a few days later at a hospital near the hotel.\textsuperscript{28} Within a few weeks, catalysed by the speed of international air travel, the infected hotel patrons spread SARS-CoV to 29 countries/regions.\textsuperscript{4,43} The main mode of spread of SARS-CoV appears to be through close contact with an infected person and transmitted via respiratory droplets or contact with fomite.\textsuperscript{44}

**Transmission in hospitals**

A super-spreading event at the Prince of Wales Hospital (PWH) in Hong Kong highlighted the nosocomial transmission potential of SARS-CoV infection. A 26-year old male (and visitor of 9th floor of Hotel M), who was admitted to a general medical ward 8A of the hospital with fever and pneumonia on March 4, 2003,\textsuperscript{45,46} led to 138 subjects (including previously healthy healthcare workers) contracting the disease within a 2-week period following exposure. An overcrowded medical ward environment, inadequate air changes in the hospital ward, and the administration of nebulized salbutamol to the index patient via a jet nebulizer for its mucociliary clearance effects appear to have contributed to this super-spreading event.\textsuperscript{45,46} SARS-CoV was detected in respiratory tract secretions, urine, faeces and tears of some patients with SARS-CoV infection.\textsuperscript{44,47} Computational fluid dynamics (CFD) analysis in conjunction with investigation of the temporal-spatial pattern of spread of SARS-CoV infection among in-patients on the affected medical ward 8A, implicated airborne transmission.\textsuperscript{48} A multi-agent modelling analysis of 1744 senarios was used to examine the contribution by different modes of transmission in the ward 8A outbreak and found that SARS-CoV most likely had spread via the combined long-range airborne and fomite routes while fomites played a non-negligible role in the transmission.\textsuperscript{49}

In Toronto, SARS-CoV was found on PCR testing of environmental air samples taken from a hospital room occupied by a patient with SARS-CoV infection, as well as from conventional surface swabs taken from a bed table, a patient’s television remote control and
a medication refrigerator door at a nurses’ station. The possibility of airborne transmission as indicated by the data emphasizes that it is imperative to take appropriate respiratory protection in addition to strict surface hygiene practices. **Table 1** shows the key timeline of spread of SARS-CoV infection from China to Singapore, Taiwan, Vietnam and Canada via Hong Kong. **Table 2** summarizes the risk factors for nosocomial transmission and super-spread ing events of SARS-CoV infection.

**Community transmission**
Opportunistic airborne transmission appears to have been responsible for a major community outbreak of SARS-CoV infection involving over 300 people in Hong Kong, in a private residential complex, the Amoy Gardens. The spread of SARS-CoV and creation of infectious aerosols that moved upward through the warm airshaft of the apartment building may have been due to dried up U-bend drainage in a bathroom floor and backflow of contaminated sewage (from a SARS patient with renal failure and diarrhea), in combination with negative pressure generated by the toilet exhaust fans. It was suggested via CFD modeling that long-range airborne transmission (>200 m) to nearby buildings was possibly caused by wind flow dispersion.

**Other routes of transmission:**
The main mode of SARS-CoV transmission is via respiratory droplets although the potential of transmission by opportunistic airborne route via aerosol-generating procedures in healthcare facilities, and environmental factors, as in the case of Amoy Gardens, is known. Other transmission routes leading to the spread of SARS-CoV included faeco-oral (presence of virus in stool, and diarrhoea as a symptom) and fomite on surfaces (virus found on surfaces in hospitals treating patients). The SARS-CoV that spread worldwide was due to a single virus strain.

**Clinical Manifestations**
A wide range of clinical manifestations are see in patients with SARS from mild, moderate to severe and rapidly progressive and fulminant disease..

**Incubation period**
The estimated mean incubation period of SARS-CoV infection was 4.6 days (95% CI, 3.8 to 5.8 days) and 95% of illness onset occurred within 10 days. The mean time from
Symptom onset to hospitalization was between 2–8 days, being shorter towards the later phase of the epidemic. The mean time from symptom onset to need for invasive mechanical ventilation (IMV) and death was 11 days and 23.7 days respectively.\textsuperscript{59}

**Symptoms:**
The major clinical features of SARS are fever, rigors, chills, myalgia, dry cough, malaise, dyspnea and headache. Sore throat, sputum production, rhinorhoea, nausea, vomiting, and dizziness are also common (Table 3).\textsuperscript{3,4,5,60-62} Watery diarrhoea was present in 40-70% of SARS patients and tended to occur about one week after illness onset.\textsuperscript{24,32} SARS-CoV was detected in the serum and cerebrospinal fluid of two patients complicated by status epilepticus.\textsuperscript{63,64} Elderly patients with SARS-CoV infection might present with poor appetite, decrease in general well-being, fracture as a result of fall,\textsuperscript{65} and confusion but some elderly subjects might not be able to mount a febrile response. In contrast, SARS-CoV infection in children aged < 12 years was generally mild while that of teenagers resembled those of adults.\textsuperscript{66} There was no mortality among young children and teenagers.\textsuperscript{66,67} SARS-CoV infection acquired during pregnancy carried a case fatality rate of 25% and was associated with a high incidence of spontaneous miscarriage, preterm delivery, and intrauterine growth retardation without perinatal SARS-CoV infection among the newborn infants.\textsuperscript{68}

Asymptomatic SARS-CoV infection was uncommon in 2003 as a meta-analysis had shown overall sero-prevalence rates of 0.1% (95% CI 0.02-0.18) for the general population and 0.23% for healthcare workers (95% CI 0.02-0.45) in comparisons to healthy blood donors, others from the general community or patients without SARS-CoV infection recruited from the healthcare setting (0.16%, 95% CI 0-0.37).\textsuperscript{69}

The clinical course of patients with SARS-CoV infection appeared to manifest in different stages.\textsuperscript{32,43,45,70} In the first week of illness of SARS-CoV infection, many patients presented with fever, dry cough, myalgia, and malaise that might improve despite the presence of lung consolidation and rising viral loads on serial samples. During the second week, many patients experienced recurrence of fever, worsening consolidation and respiratory failure while about 20% of patients progressed to ARDS requiring IMV.\textsuperscript{32,43,45} Peaking of viral load on day 10 of illness\textsuperscript{32} corresponded temporally to peaking of the extent of consolidation
radiographically, and a maximal risk of nosocomial transmission, particularly to healthcare workers.\textsuperscript{72}

**Diagnosis and Investigations**

**Laboratory Diagnosis**

The detection rates for SARS-CoV infection in 2003 using reverse transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal specimens, urine, stool and blood are shown in table 4.\textsuperscript{32,73-75} It is important to collect a combination of upper respiratory (nasal, pharyngeal, nasopharyngeal), lower respiratory (higher yield because of higher viral levels, eg, sputum, tracheal aspirate, bronchoalveolar lavage), blood, and fecal specimens in order to maximize the chance of detection. A single negative test in an upper respiratory specimen does not rule out the diagnosis. Since viral kinetics demonstrated an inverted V-shape curve peaking on day 10 of illness with progressive decrease in rates of viral shedding from nasopharynx, stool, and urine (which might persist up to day 21), clinical progression during the second week was thought to be related to immune-mediated lung injury.\textsuperscript{32}

Specimens for viral culture require processing in biosafety level 3 facilities but the results take too long to assist acute clinical management. Serologic diagnosis is largely retrospective and useful for epidemiologic surveillance purposes. A more robust IgG response was observed in severe SARS-CoV infections as reflected by higher IgG levels in patients who required supplemental oxygen, ICU-admission, patients with negative pre-discharge fecal RT-PCR results, and those with lymphopenia at presentation.\textsuperscript{76} A study in Beijing has shown that 6 years following SARS-CoV infection, specific IgG Ab to SARS-CoV eventually disappeared and peripheral memory B cell responses became undetectable in recovered SARS patients but specific T cell anamnestic responses could be maintained for at least 6 years.\textsuperscript{77} Absolute lymphopenia (lymphocyte count<1.0 x10\textsuperscript{9}/L) was observed in 98% of cases of SARS-CoV infection while low CD4 and CD8 lymphocyte counts on hospitalization were associated with adverse clinical outcomes.\textsuperscript{78} Liver dysfunction with abnormal alanine transaminases (ALT) was noted in 29.6% of patients on presentation but increased to 75.9%
of those receiving systemic corticosteroid and ribavirin for treatment of SARS-CoV infection.79

**Radiological features**
The radiographic features of SARS-CoV infection were basically non-specific. About a quarter of patients might have unremarkable chest radiographs initially,3,4,5,60 with non-specific changes, ranging from normal to peribronchial thickening and ill-defined airspace shadowing (Figure 2).

High resolution computer tomography (HRCT) of thorax could detect small parenchymal lesions early.80 Common HRCT findings included interlobular septal and intra-lobular interstitial thickening, consolidation, and ground-glass opacification, predominantly involving peripheral lung fields and lower lobes, with features closely resembling those found in COP45,80 (Figure 3). In an ICU case series of critically ill patients, 12% of patients developed pneumo-mediastinum spontaneously while 20% of patients developed evidence of ARDS over a period of 3 weeks.32 Despite the use of lung protective IMV with a low tidal volume, barotrauma occurred in 26% of critically ill cases of SARS-CoV infection, possibly due to decreased lung compliance.81

**Prognostic markers and Outcome**
The prognostic factors associated with a poor outcome (ICU admission or death) in SARS-CoV infection are summarized in table 5.32,45,60-62,73-75 Infants (preterm or full-term) born to mothers infected with SARS-CoV infection were neither shedding SARS-CoV nor clinically infected in the postnatal period.82 The clinical course of SARS-CoV infection in elderly patients, particularly those with comorbidities was typically fulminant and often fatal.

**Antiviral therapy and other potential treatments**

**Ribavirin**
Ribavirin, a nucleoside analogue, was widely prescribed for treatment of SARS-CoV infection in 2003.32,45,60,61 Nevertheless, ribavirin monotherapy had minimal activity against SARS-CoV with concentrations that could be achieved in the clinical setting, and it led to significant haemolysis in many patients.32,45,83
**Antiviral therapy**

The efficacy of antiviral agents including ribavirin, protease inhibitors and interferon that were used to treat patients with SARS-CoV infection in 2003 is summarized in table 6.\textsuperscript{60,83-86} Due to lack of prospective randomized, placebo-controlled clinical trial data, none of these therapies have proven benefit. Good supportive care remains the main stay of treatment for SARS-CoV infection.

**Systemic Corticosteroids**

Systemic corticosteroid in the form of intravenous pulse methylprednisolone (MP) was given to some patients with SARS-CoV infection for several reasons.\textsuperscript{32,45,61,62,83} Firstly, there was an assumption that clinical progression of pneumonia and respiratory failure in association with peaking of SARS-CoV viral load might be mediated by the host inflammatory response.\textsuperscript{32,71} Also in many patients there were HRCT\textsuperscript{3,45,80} and histological features of COP, which was a steroid-responsive condition.\textsuperscript{30} Systemic corticosteroids significantly reduced IL-8, MCP-1, and IP-10 concentrations from 5 to 8 days after treatment in 20 adults with SARS-CoV infection.\textsuperscript{34} In addition, in patients with fatal SARS-CoV infection, there was evidence of haemo-phagocytosis in the lungs,\textsuperscript{28} attributed to cytokine dysregulation.\textsuperscript{87} Intervention with systemic corticosteroids was thus given in order to modulate these immune responses.

Although there was clinical improvement in some patients with resolution of fever and lung consolidation following treatment with IV pulsed MP,\textsuperscript{3,83} a retrospective cohort analysis in Hong Kong showed that the use of pulsed MP was actually associated with an increased risk of 30-day mortality (adjusted OR 26.0, 95% CI 4.4 to 154.8).\textsuperscript{88} In addition, prolonged use of systemic corticosteroid therapy could increase the risk of nosocomial infections such as disseminated fungal disease,\textsuperscript{89} metabolic derangements, psychosis, and osteonecrosis.\textsuperscript{90} A randomized controlled trial (RCT) showed that plasma SARS-CoV RNA concentrations in the second and third weeks of illness were higher in patients given initial hydrocortisone (n = 10) than those given normal saline as control (n = 7) during early clinical course of illness. The data suggest that systemic corticosteroids given early in the course of SARS-CoV infection might prolong viraemia.\textsuperscript{91} A systematic review concluded that systemic
corticosteroid treatment was not associated with definite benefits and was potentially harmful.\textsuperscript{92}

\textit{Convalescent Plasma/passive immunotherapy}
Convalescent plasma, donated mostly by healthcare workers who had fully recovered from SARS-CoV infection, appeared clinically useful for treating other patients with progressive SARS-CoV infection.\textsuperscript{93,94} In a study comparing patients with SARS-CoV infection who did and did not receive convalescent plasma, 19 patients who received such therapy had higher survival rate (100\% vs 66.2\%) and higher discharge rate (77.8\% vs 23.0\%) compared with 21 controls.\textsuperscript{94} An exploratory post-hoc meta-analysis of studies of SARS-CoV infection and severe influenza showed a significant reduction in the pooled odds of mortality following convalescent plasma versus placebo or no treatment (OR 0.25; 95\%CI 0.14 to 0.45).\textsuperscript{95} Early administration of convalescent plasma appeared more effective as among 80 patients with SARS-CoV infection who had been given convalescent plasma at PWH, the discharge rate at day 22 was 58.3\% for patients (n=48) treated within 14 days of illness onset vs 15.6\% for those (n=32) treated beyond 14 days.\textsuperscript{93} In the absence of well proven and effective antiviral therapy, convalescent plasma and human monoclonal antibody are worth further study against SARS-CoV if it returns.

\textbf{Prevention}

\textit{Vaccines}
The S protein of SARS-CoV plays an important role in mediating viral infection via receptor binding and membrane fusion between the virion and the host cell, and is a major epitope. An adenoviral-based vaccine could induce strong SARS-CoV specific immune responses in rhesus macaques, and hold promise for development of a protective vaccine against SARS-CoV.\textsuperscript{96} Other investigators reported the S gene DNA vaccine could induce the production of specific IgG antibody against SARS-CoV efficiently in mice with seroconversion ratio of 75\% after 3 doses of immunization,\textsuperscript{97} while viral replication was reduced by more than 6 orders of magnitude in the lungs of mice vaccinated with S plasmid DNA expression vectors, and protection was mediated by a humoral immune mechanism.\textsuperscript{98} Recombinant S protein
exhibited antigenicity and receptor-binding ability, while synthetic peptides eliciting specific antibodies against SARS-CoV S protein might provide another approach for further developing SARS vaccine.

**General Preventive Measures**

Prevention of transmission is crucial for managing this highly infectious disease. The primary mode of transmission of SARS-CoV infection is through direct contact and exposure to infectious respiratory droplets, or fomites, and it is therefore necessary to maintain good personal and environmental hygiene, and to implement stringent contact and droplet precautions among the healthcare workers. To prevent community transmission, contact tracing, quarantine/isolation of close contacts and public education are important measures. Between 16 Dec 2003 and 30 Jan 2004, 4 new cases of SARS-CoV infection emerged in Guangdong and a link was established between humans and small wild animals. The Guangdong government and Department of Public Health took public health measures and implemented strict controls over the wildlife market, including banning the rearing, transport, slaughter, sales, and food processing of small wild mammals and civet cats.

**Hospital Infection Control Measures**

Nosoconial transmission was a hallmark of SARS-CoV infection in 2003, with 1706 out of 8096 (21%) of SARS patients globally being healthcare workers. A plausible reason is that viral loads reached their highest levels 10 days from disease onset at the same time when the patient was most symptomatic and dyspneic, and observation/treatment of these patients at a close distance became necessary by the healthcare workers. Different medical wards should be designated for patient triage (for undifferentiated fever), confirmed SARS cases, and other patients in whom SARS has been ruled out. In the event of a late detection of a nosocomial outbreak, hospital closure is required to contain onward disease transmission. However, outbreaks that are detected early and limited to few patients, may be managed by isolating the infected patients in place or alternatively, relocating the affected to a designated location. Early case detection followed by isolation should ideally be performed in negative pressure isolation rooms if available. Implementing droplet precautions and contact precautions appeared adequate to reduce the risk of infection after general exposure to patients with mild SARS-CoV infection. Airborne precautions (hand hygiene, gown, gloves,
N95 masks, eye protection) should be implemented if aerosol-generating procedures are to be undertaken.\textsuperscript{100}

**Conclusions**

The SARS epidemic demonstrated that novel highly pathogenic viruses crossing the animal-health barrier remain a major threat to global health security. SARS posed a major challenge for global public health services due to its sudden appearance, rapid spread and disappearance. The knowledge and lessons learnt from SARS-CoV epidemiology, mode of transmission, clinical course, complications, clinical management, predictors of poor outcome, and infection control have been invaluable.

Although no major outbreaks have occurred since the last reported SARS cases involving laboratory personnel in Singapore and Taiwan, and four residents in Guangdong, an epidemic is possible at any time. Whether SARS will reappear and cause another pandemic remains unknown. The appearance of MERS-CoV in 2012 as another highly pathogenic zoonotic coronavirus which continues to circulate in the Middle East reminds physicians and public health authorities that the threat of coronavirus outbreaks is ever present.
REFERENCES


LEGENDS TO FIGURES

Figure 1: Global distribution of SARS

Figure 2: Chest radiograph of a patient showing opacities at the right lower zone and left mid and lower zones

Figure 3: Chest tomography of another patient with ground glass opacity at the anterolateral segment of the left lower lobe

Figure 1: Global distribution of SARS
Table 1. Important Timeline of Spread of SARS-CoV infection from China to Canada, Vietnam, Taiwan, Vietnam and Singapore via Hong Kong

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 November 2002</td>
<td>First known case of atypical pneumonia in Foshan City, Guangdong Province, China, but aetiology not identified until much later.</td>
</tr>
<tr>
<td>11 February 2003</td>
<td>WHO received reports from the Chinese Ministry of Health of an outbreak of acute respiratory syndrome with 300 cases and 5 deaths in Guangdong Province.</td>
</tr>
<tr>
<td>21 February 2003</td>
<td>A 64-year-old medical doctor from Zhongshan University in Guangzhou (Guangdong Province) arrived in Hong Kong to attend a wedding and checked into the ninth floor of Hotel M (room 911).</td>
</tr>
<tr>
<td>22 February, 2003</td>
<td>The Guangdong doctor was admitted to the intensive care unit at the Kwong Wah Hospital in Hong Kong with respiratory failure (he had previously treated patients with atypical pneumonia in Guangdong). He warned medical staff that he might have contracted a “very virulent disease” with onset of symptoms on 15 February 2003.</td>
</tr>
<tr>
<td>26 February, 2003</td>
<td>A 48-year-old Chinese-American businessman was admitted to the French Hospital in Hanoi with a 3-day history of fever and respiratory symptoms. He travelled to Hong Kong on 17 February, departed for Hanoi on 23 February, and fell ill there. Shortly before his departure from Hong Kong, he had stayed on the ninth floor of the Metropole Hotel in a room across the hall from the Guangdong doctor.</td>
</tr>
<tr>
<td>1 March, 2003</td>
<td>A 26-year-old woman was admitted to a hospital in Singapore with respiratory symptoms. A resident of Singapore, she was a guest on the ninth floor of the Hotel Metropole in Hong Kong from 21 to 25 February.</td>
</tr>
<tr>
<td>4 March, 2003</td>
<td>The Guangdong doctor died of atypical pneumonia at Kwong Wah Hospital in HK.</td>
</tr>
<tr>
<td>5 March, 2003</td>
<td>In Hanoi, the Chinese-American businessman, in a stable but critical condition, was air medivaced to the Princess Margaret Hospital in Hong Kong. Seven healthcare workers who had cared for him in Hanoi became ill.</td>
</tr>
<tr>
<td></td>
<td>A 78-year-old Toronto woman, who had checked out of the Hotel Metropole in HK on 23 Feb, died at Toronto’s Scarborough Grace Hospital. Five members of her family were infected and admitted to the hospital. Her son, aged 43, fell ill on February 27, 2003 and was consequently admitted to a community hospital on March 7, 2003, leading to a major nosocomial outbreak. Subsequent chains of disease transmissions resulted in numerous hospital outbreaks that involved 257 people.</td>
</tr>
<tr>
<td>7 March, 2003</td>
<td>Healthcare workers at Hong Kong’s Prince of Wales Hospital started to complain of respiratory tract infection, progressing to pneumonia. All had an identifiable link with Ward 8A.</td>
</tr>
<tr>
<td>8 March, 2003</td>
<td>In Taiwan, the source of SARS-CoV infection was a 54-year old merchant who returned to Taipei via Hong Kong after visiting Guangdong on February 5, 2003. By February 25, 2003 he had developed fever, myalgia and dry cough but was not hospitalized until March 8, 2003.</td>
</tr>
<tr>
<td>12 March, 2003</td>
<td>WHO issued a global alert about cases of severe atypical pneumonia following mounting reports of spread among...</td>
</tr>
</tbody>
</table>
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staff at hospitals in Hong Kong and Hanoi.
– At the French Hospital in Hanoi, 26 staff had symptoms. Of these, 25 had either pneumonia or acute respiratory syndrome, and 5 in critical condition. The hospital was closed to new admissions.
– Hong Kong health authorities formally reported an outbreak of unidentified flu-like illness among hospital staff at the Prince of Wales Hospital. As of midnight 11 March, 50 healthcare workers had been screened, 23 were found to have febrile illness, and 8 showed early chest X-ray signs of pneumonia. A 26 yr old man, who had visited an acquaintance staying on the ninth floor of the Metropole Hotel from 15 to 23 February, was the source of this hospital outbreak following subsequent epidemiological investigation.

13 March, 2003
– The Ministry of Health in Singapore reported three cases of atypical pneumonia in young women who had recently returned to Singapore after travelling to Hong Kong. All had stayed on the ninth floor of the Metropole Hotel in late February.

15 March, 2003
– WHO issued a travel advisory as evidence mounted that SARS was spreading by air travel along international routes. WHO named the mysterious illness after its symptoms: severe acute respiratory syndrome (SARS) and declared it “a worldwide health threat.”

26 March, 2003
The arrival of an infected resident of the Amoy Gardens from Hong Kong to Taiwan on March 26, 2003 led to an escalation of SARS-CoV cases in Taiwan from mid-April 2003. Subsequent phylogenetic analysis of both Taiwan and Hong Kong outbreaks revealed the same strain of virus.

28 April, 2003
– In Hanoi, there was a reported total of 63 cases of SARS-CoV infection before the outbreak was declared to be over on April 28, 2003

5 May, 2003
The SARS-CoV outbreak in Singapore was characterized by rapid nosocomial transmission involving a large number of healthcare workers [97 out of 238 probable SARS cases (41 %)] and several super-spreading events. Transmission of SARS was finally brought to an end, with no new cases after May 5, 2003.

14 May, 2003
Toronto was initially removed from the WHO list of areas with recent local SARS transmission and there was a province-wide scaling back of SARS control measures, such as fever surveillance and monitoring of respiratory symptoms in existing in-patients and visitors. However, one month after the SARS-CoV outbreak was thought to have ended, another surge of cases arose in a Toronto rehabilitation hospital involving HCWs, visitors, and patients who had been exposed to hospitalized patients with undiagnosed SARS-CoV infection.

2 July, 2003
Toronto was finally free from local transmission.

5 July, 2003
It was finally announced by the WHO that the transmission chain of SARS-CoV in Taiwan was broken, bringing an end to the SARS-CoV epidemic.
Table 2) Risk factors of nosocomial transmission of SARS-CoV infection

<table>
<thead>
<tr>
<th>Risk Factors of Super-Spreading Nosocomial Outbreaks of SARS:52</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Performance of resuscitation (OR 3.81, 95%CI 1.04-13.87, p=0.04)</td>
</tr>
<tr>
<td>• Staff working while experiencing symptoms (OR 10.55, 95%CI 2.28-48.87, p=0.003)</td>
</tr>
<tr>
<td>• SARS patients requiring oxygen therapy at least 6L/min (OR 4.30, 95%CI 1.00-18.43, p=0.05)</td>
</tr>
<tr>
<td>• SARS patients requiring non-invasive positive pressure ventilation (OR 11.82, 95%CI 1.97-70.80, p=0.007)</td>
</tr>
<tr>
<td>• Minimum distance between beds &lt;1m (OR 6.98, 95%CI 1.68-28.75, p=0.008)</td>
</tr>
<tr>
<td>• Washing or changing facilities for staff (OR 0.12, 95%CI 0.02-0.97, p=0.05)</td>
</tr>
</tbody>
</table>

b) Respiratory procedures associated with increased risk of transmission to healthcare workers53

Procedures reported to present an increased risk of transmission included: [n; pooled OR(95%CI)]

- Tracheal intubation [n=4 cohorts; 6.6 (2.3, 18.9), and n=4 case-control; 6.6 (4.1, 10.6)],
- Non-invasive ventilation [n=2 cohorts; OR 3.1(1.4, 6.8)],
- Tracheotomy [n=1 case-control; 4.2 (1.5, 11.5)] a
- Manual ventilation before intubation [n=1 cohort; OR 2.8 (1.3, 6.4)]
<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of patients with symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent fever &gt; 38C</td>
<td>99-100</td>
</tr>
<tr>
<td>Non-productive cough</td>
<td>57-75</td>
</tr>
<tr>
<td>Myalgia</td>
<td>45-61</td>
</tr>
<tr>
<td>Chills/rigor</td>
<td>15-73</td>
</tr>
<tr>
<td>Headache</td>
<td>20-56</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>40-42</td>
</tr>
<tr>
<td>Malaise</td>
<td>31-45</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>20-35</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20-25</td>
</tr>
<tr>
<td>Sore throat</td>
<td>13-25</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.2-43</td>
</tr>
<tr>
<td>Sputum production</td>
<td>4.9-29</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>2.1-23</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10.4</td>
</tr>
</tbody>
</table>
Table 4. Diagnostic Tests for SARS-CoV \(^{32,73-75}\)

<table>
<thead>
<tr>
<th>RT-PCR</th>
<th>Detection rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal aspirate</td>
<td>Conventional RTPCR: 32% Day 3, 68% Day 14.(^{32})</td>
</tr>
<tr>
<td></td>
<td>Second-generation with real-time quantitative RTPCR</td>
</tr>
<tr>
<td></td>
<td>assay: 80% during first 3 days(^{73})</td>
</tr>
<tr>
<td>Stool(^{32})</td>
<td>97% Day 14 of illness</td>
</tr>
<tr>
<td>Urine(^{32})</td>
<td>42% Day 15 of illness</td>
</tr>
<tr>
<td>Real-time quantitative Serum SARS-CoV RNA(^{74,75})</td>
<td>80% Day 1, 75% Day 7, 45% Day 14</td>
</tr>
<tr>
<td>Serology IgG seroconversion to SARS-CoV(^{32})</td>
<td>15% Day 15, 60% Day 21, &gt;90% Day 28</td>
</tr>
</tbody>
</table>
Table 5. Poor prognostic factors associated with ICU admission and/or deaths in patients with SARS-CoV infection\textsuperscript{32,45,60-62,74,75}

<table>
<thead>
<tr>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Age\textsuperscript{32,45,58,61,62}</td>
</tr>
<tr>
<td>Viral Loads: High SARS-CoV viral loads in nasopharyngeal secretions,\textsuperscript{32} High plasma SARS-CoV concentrations\textsuperscript{74,75}</td>
</tr>
<tr>
<td>Co-morbidities: Chronic hepatitis B,\textsuperscript{32} Diabetes mellitus or other co-morbid conditions,\textsuperscript{60,61}</td>
</tr>
<tr>
<td>Laboratory markers: High peak LDH,\textsuperscript{45} High initial LDH level,\textsuperscript{62} High neutrophil count on presentation,\textsuperscript{45,62} Low counts of CD4 and CD8 at presentation,\textsuperscript{78}</td>
</tr>
</tbody>
</table>
Table 6. Agents applied for treatment of humans with SARS-CoV infection in 2003

<table>
<thead>
<tr>
<th>Agents</th>
<th>Description</th>
</tr>
</thead>
</table>
| Ribavirin   | Ribavirin given at 1.2g tds orally for 2 weeks resulted in a drop in hemoglobin of > 2 g/dL from baseline in 59% of patients, with evidence of hemolysis documented in 36%.

Based on a higher dosage of ribavirin for treating haemorrhagic fever virus, patients with SARS-CoV infection in Toronto developed more toxicity, including elevated transaminases and bradycardia.

| Protease inhibitor | Two retrospective, matched cohort studies have compared the clinical outcome of patients who received protease inhibitor (lopinavir 400 mg/ritonavir 100 mg) in addition to ribavirin, either as initial therapy within 5 days of onset of symptoms or as rescue therapy after pulse methylprednisolone treatment for worsening respiratory symptoms; these were compared with historical controls who received ribavirin alone as initial anti-viral therapy.

The addition of lopinavir/ritonavir as initial therapy was associated with reduced overall death rate (2.3%) and intubation rate (0%), in comparisons with a matched cohort that received standard treatment (15.6% and 11%) respectively; there was also evidence of reduction in viral loads. Other beneficial effects included a reduction in methylprednisolone use and less nosocomial infections.

However, the subgroup that had received lopinavir/ritonavir as rescue therapy was no better than the matched cohort, and received a higher mean dose of methylprednisolone. The improved clinical outcome in patients that received lopinavir/ritonavir as part of the initial therapy is supported by the observations that both peak (9.6 ug/ml) and trough (5.5 ug/ml) serum concentrations of lopinavir could inhibit the virus.

| Interferon   | In an uncontrolled study in Toronto, interferon-alfacon-1 given within 5 days of illness resulted in improved oxygen saturation, more rapid resolution of radiographic lung opacities, and lower rates of intubation (11.1% vs 23.1%) and death (0.0% vs 7.7%); however, the sample size was small (n=9 vs 13) and confounded by the concomitant use of systemic corticosteroid. |