Severe Acute Respiratory Syndrome (SARS)

Dennis J. Cleri, MD, FACP, FAAM, FIDSA[a,b,c,]*,
Anthony J. Ricketti, MD, FCCP[a,b,c,d], John R. Vernaleo, MD, FACP[e]

To-morrow, and to-morrow, and to-morrow,
Creeps in this petty pace from day to day,
To the last syllable of recorded time;
And all our yesterdays have lighted fools
The way to dusty death. Out, out, brief candle!
Life's but a walking shadow
William Shakespeare, Macbeth

INTRODUCTION AND VIROLOGY

From November 2002 to July 2003, severe respiratory distress syndrome (SARS) quickly spread from Foshan (Shunde district), Guangdong Province in the People's Republic of China to 33 other countries or regions on 5 continents.[1–3] The details of the rapidity of the early epidemic are given by Lam and colleagues.[4] There were 8447 cases, 21% occurring in health care workers (HCWs), and 813 deaths (9.6% overall mortality) by the time SARS was contained in July 2003.[1,5–7] In the Hong Kong and Hanoi outbreaks, 46% and 63% of cases occurred in HCWs, respectively.[7] The case-fatality rate in 2003 was estimated at 13.2% for patients younger than 60 years and 50% for patients more than 60 years of age. Fifty percent of patients with acute respiratory distress syndrome (ARDS) died.[2,3,8] Laboratory-acquired cases resulted in transmission to family contacts.[2] A few patients were "superspreaders" of the virus.[3] In 1 hospital, exposure to a single patient resulted in infection in 138 patients and HCWs.[9] Two hundred fifty-two cases were reported in Canada (February 23 to June 12, 2003) and 29 cases were reported in the United States (February 24 to July 13, 2003).[1,3]

The pathogen, the human coronavirus (CoV) group 2b, SARS-CoV, is of animal origin.[10–12] The SARS-like-CoV (SL-CoV) virus from animal hosts has a nucleotide homology greater than 99% with SARS-CoV.[13] From virus sequence data, it seems that the masked (Himalayan) palm civet (*Paguma larvata*) acted as an amplification host. The epidemic strains (including SARS-Urbani) evolved because of civet-human interaction in Chinese animal markets.[14] Serologic evidence of natural SL-CoV infection is also found in the Chinese ferret-badger (*Melogale moschata*). SARS-CoV strains from the 2002 to 2003 outbreak (referred to as the "late human SARS-CoV" strains based on presumed evolutionary characteristics) differ from the strains from the 2003 to 2004 epidemic ("early human SARS-CoV" strains) in (1) spike protein genetic homogeneity, rate of nonsynonymous mutation, and binding affinity to angiotensin-converting enzyme 2 (ACE-2); (2) severity of disease; (3) epidemic potential; (4) transmission (animal/human-to-human, early strains (2003–2004 isolates); human-to-human, late strains (2002–2003 isolates)); and (5) the presence of a 415 nucleotide deletion in some of the late strains.[13]

There are 26 known species of CoV infecting 36 animal species.[10,15,16] In addition to SARS-CoV, 4 other human CoVs (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1) cause illness. SL-CoV does not cause disease in humans. HCoV-NL63 and HCoV-HKU1 have a worldwide distribution, and cause respiratory tract infections, especially in the winter months.[17] A survey of nasopharyngeal swabs from patients with acute respiratory tract infections (Hong Kong, n = 4181), found 2.1% to be infected with 1 of these other (non-SARS-CoV) viruses.[11] In children (in France), these pathogens were isolated from 9.8% of respiratory specimens from hospitalized children and immunocompromised adults.[18,19]

Evidence that SARS-CoV is a new virus of animal origin is based on: (1) genetic sequencing; (2) retrospective human serologic studies finding no evidence of SARS-CoV or related viral infections; (3) during the 2002 to 2003 SARS epidemic, serologic surveys among market traders found a higher seroprevalence for antibodies against SARS-CoV or related viruses amongst animal traders than controls; (4) the earliest SARS cases lived near produce markets but not near farms, and almost half were food handlers with likely animal contact; and, (5) SARS-CoVs isolated from animals in markets were almost identical to human isolates.[20]

CoVs, named for their crownlike morphology, are 80 to 160 nm, positive-sense single stranded RNA viruses with helical nucleocapsids. They belong to the

Coronaviridae family of the Nidovirales order, and have the largest known RNA genome, increasing the likelihood of genetic variation.[10,21] In wild and domestic animals, CoVs cause mild to severe enteritis, respiratory, neurologic, and systemic disease.[21] In humans, they cause the common cold in addition to SARS (SARS-CoV).[10] Necrotizing enterocolitis in newborns has been associated with a CoV-like agent.[22] Animals and humans are infected by group 1 and 2 CoVs, and birds are infected by group 3.[10] Rodents and bats are also infected by CoVs. Group 2 CoVs include human CoVs (HCoV-OC43 and HCoV-HkU1), mouse hepatitis virus, rat CoV, bovine CoV, porcine hemaglutinating encephalomyelitis virus, equine CoV, and canine respiratory CoV.[10] Interspecies transmission of CoVs is well documented. Animals and birds may act as natural reservoirs for CoV-related diseases in domestic animals and humans. A study conducted by the US Centers for Disease Control and Prevention (CDC) found no evidence of SARS-CoV transmission from bats to humans among bat biologists who were "always" or "most of the time" (66%–68% of test subjects) exposed to bat blood, saliva, tissue, bites, or scratches.[23] The virology and pathogenesis of SARS-CoV are discussed by Weiss and Navas-Martin.[21]

SARS-CoV has been isolated from Himalayan (masked) palm civets (*Paguma larvata*), raccoon dogs (*Nyctereutes procyonides*), and Chinese ferret-badgers (*Melogale moschata*) in wild live markets in (Shenzhen) China.[6,12,20,24] More than 10 mammalian species are susceptible to SARS-CoV, including cynomolgus macaque (*Macaca facicularis*), rhesus macaque (*Macaca mulatta*), African green monkey (*Cercopithecus aethiops*), ferret (*Mustela furo*), golden hamster (*Mesocricetus auratus*), guinea pig (*Cavia porcellus*), mouse (*Mus musculus*), rat (*Rattus rattus*), domestic cat (*Felis domesticus*), and pig (*Sus scrofa*).[21]

The common marmoset is susceptible to SARS-CoV. It develops disease similar to human illness (pneumonia, hepatitis, mild colitis with watery diarrhea).[2]

SL-CoV has been isolated from Chinese horseshoe bat species (*Rhinolophus pearsoni*, *R macrotis*, *R pussilus*, and *R ferrumequinum*) and the cave-dwelling fruit bat (*Rousettus leschenault*).[5,7,12] Serologic or polymerase chain reaction (PCR) evidence of infection by closely related SARS-CoV viruses in bats found in Chinese provinces 1000 to 2000 km apart and in Hong Kong strongly suggest that bats are the natural reservoir. Other CoVs have been isolated from bat species from the People's Republic of China: *R sinicus*, *R pearsoni*, *R ferrumequinum*, *R macrotis*, *R ferrumequinum*, *Myotis ricketti*, *Miniopterus magnater*, *M pusillus*, *M schreibersii*, *Scolophlus kuhlii*, *Tylonycteris pachypus*, *Pipistrelius abramus*, *and P pipistrellus*.[20,25] In the United States (in wild and zoo-kept animals), CoVs have been isolated from bats (*Myotis occultus*, *Eptesicus fuscus*), sambar deer (*Cevus unicolor*), white-tailed deer (*Odocoileus virginianus*), waterbuck (*Kobus ellipsipyrmnus*), elk (*Cervus elephus*), caribou (*Rangifer tarandus*), sitatunga (*Tragelaphus spekei*), giraffe (*Giraffa camelopardalis*), and musk oxen (*Ovibus moschatus*).[10,23]

Bats are sold in the live markets in southern China for consumption and use in traditional medicine. No one has observed civets becoming ill from naturally occurring infection. However, when injected with SARS-CoV, they develop fever, lethargy, loss of aggressiveness, and decreased appetite. This result and there being no evidence of infection in wild and farmed civets make them an unlikely animal reservoir.[12,20]

The SL-CoV has greater genetic variation than SARS-CoV. Pteropid bats (flying foxes or fruit bats) are reservoirs for Hendra and Nipah viruses, which are emerging infections in Australia and Southeast Asia. In the henipaviruses, the bat-derived viruses have greater genetic diversity than the viruses isolated in the Nipah virus outbreaks in Malaysia and Bangladesh in 1999 and 2004.[12]

Bats tolerate these and other viral infections without any outward signs,[12,20] which suggests that civets became infected in the markets while captive in proximity to the bats.[26] The civet (a "naive" species) in turn infects man.[12]

Hamsters, guinea pigs, young mice (4–6 weeks old), rats, cats, and pigs remain asymptomatic when experimentally infected with SARS-CoV. Rats are a particular problem as they are ubiquitous. The only animal contact of the first human case in 2004 in Guangdong was rats. Birds are not susceptible to SARS-CoV infection.[20,21]

Of the 3 structural membrane proteins of SARS-CoV, the spike (S) protein has a 76% similarity with bat SL-CoV, and 78% similarity with civet CoV. The membrane (M) and envelope (E) proteins have 96% and 100% similarity, respectively. Variation in the S protein is believed to be responsible for host range, interspecies transmission, and adaptation.[21,24]

HISTORY

There are more things in heaven and earth, Horatio,
Than are dreamt of in your philosophy.
William Shakespeare, Hamlet

Dr Carlo Urbani of the World Health Organization (WHO) and President of the Italian branch of Médecins Sans Frontières first identified the disease in an American businessman hospitalized in Hanoi, Vietnam, in February 2003. WHO designated the new disease "SARS" on March 15, 2003. Dr Urbani died of SARS on March 29 that same year.[1,4] Most of the cases were reported from China (5327) and the Far East (Hong Kong: 1755; Taiwan: 678; and Singapore: 206).[1,3]

The pathogen, a novel CoV, was isolated in Vero-cell culture and detected by reverse transcriptase PCR (RT-PCR) from patients' respiratory secretions. The disease was reproduced by inoculation into cynomolgus macaques, and identified in these animals by negative-contrast electron microscopy and RT-PCR. The genome has been completely sequenced, and that analysis indicates that SARS-CoV is not closely related to any of the other 3 CoV groups.[1]

PATHOLOGY

At post mortem, the highest concentration of virus is found in the lungs and small bowel. This is probably related to the density of SARS-CoV receptors.[27] The alveolar epithelium has the highest intensity of infection followed by alveolar macrophages. There is little involvement of the bronchiolar epithelium, and no involvement of the bronchial epithelium or regional lymph nodes.[28] Other autopsy studies reveal little pathology in the upper respiratory tract, and no peribronchial or hilar adenopathy. There are limited serous pleural effusions, and pronounced pulmonary edema and consolidation.[28]

Histologically, there is diffuse alveolar damage, pulmonary edema, and hyaline membranes. Some areas reveal interstitial thickening. Some patients display intraalveolar organization of exudates and granulation tissue in the small airways, especially in the subpleural areas. Atypical pneumocytes, either multinucleated giant cells or cells with large atypical nuclei, are present in most patients. Vascular fibrin thrombi are common and often accompanied by pulmonary infarcts.[29] Some patients have evidence of bacterial (including methicillin-resistant *Staphylococcus aureus* and *Stenotrophomonas maltophilia*), fungal (*Aspergillus* and *Candida* species) or viral

(cytomegalovirus) superinfections. Viral-like particles that represent viral nucleocapsids are seen in scanty pneumocytes.[9,29–31]

Spleen and lymph node histology reveals lymphocyte depletion, and white pulp atrophy in the spleen.[30]

Pathologic changes from biopsy or autopsy specimens from the gastrointestinal tract are minimal (mucosal lymphoid depletion), but evidence of viral replication is found in the small and large intestine.[30,32]

In patients who died with acute renal failure (ARF), pathology reveals acute tubular necrosis without glomerular disease.[33]

In the central nervous system, there was edema, and degeneration of neurons with evidence of viral infection. Bone marrow abnormalities, in some but not all patients, included hemophagocytosis. Necrosis and infiltration of the adrenal gland with monocytes and lymphocytes, destruction of follicular epithelial cells in the thyroid, germ cell destruction, and apoptotic spermatogenetic cells in the testes, and edema and atrophy of myocardial fibers were seen.[30] Myofiber degeneration with myofiber necrosis, macrophage infiltration, myofiber atrophy, and rare regenerative fibers were present. Necrotic fibers accumulated IgG, IgM, C3, and fibrinogen, but without other chronic inflammatory or lymphocytic infiltration.[34]

In animal models (cats and ferrets), ACE-2 and CD209L (also known as L-SIGN, a SARS-CoV binding receptor that mediates proteasome-dependent viral degradation and is expressed in cytokeratin$^+$ respiratory epithelia) are the SARS-CoV receptors in the respiratory tract, although ACE-2 is the most efficient.[2,35] SARS-CoV antigen expression and lesions developed in the respiratory tract of animals 4 days post inoculation. Diffuse alveolar damage associated with SARS-CoV antigen expression evolved in all infected animals. Cats developed a unique tracheobronchoadenitis. Antigen expression was seen in type I and II pneumocytes and serous cells of the tracheobronchial submucosal glands in cats, and serous epithelial cells and type II pneumocytes in ferrets. The difference between these animal models and humans is that humans develop syncytial and hyaline membranes.[35]

The renin-angiotensin system plays an important role in the pathogenesis of pulmonary hypertension and pulmonary fibrosis.[36] ACE cleaves angiotensin I, producing the peptide, angiotensin II. ACE-2 reduces angiotensin II levels. ACE-2 knockout mouse studies demonstrate that ACE-2 protects the animals from ARDS. SARS-CoV injections, and injections of SARS-CoV S protein reduces ACE-2 expression and worsens ARDS.[37,38]

ACE-2 is highly expressed in the enterocytes of the small intestine, and this organ becomes infected with SARS-CoV. In other organs, cell types without ACE-2 expression may become infected. Some endothelial cells, which express ACE-2 to a high level, do not become infected.[39]

Another postulated pathologic mechanism is that human long interspersed nuclear element 1 endonuclease domain protein seems to be the target of SARS-associated autoantibodies. These antibodies were found in 40.9% of patients with SARS.[40]

On presentation, virus may be detected in patients by RT-PCR in nasopharyngeal aspirates (80%), stool (84.4%), and urine (33.3%). All 3 sites were positive in 28.9% of patients, and 40% of patients remained positive (at least at 1 site) on discharge.[41] Shedding peaks 10 days after the onset of symptoms.[42] Patients do not stop shedding for another 13 days (range 2–60 days). The median time to becoming RT-PCR negative was 30 days (range 2–81 days).[41]

The virus survives drying on inanimate surfaces for as long as 6 days.[43] It is inactivated by 500 ppm hypochlorite (laundry bleach), exposure for 5 minutes or less to 75% ethanol, and household detergents. Disinfection of waste systems, elimination of

rodents and cockroaches, and care in garbage disposal are all considered important in preventing infection.[5,43–47] Standard disinfectants or detergent disinfectants approved by the Environmental Protection Agency are recommended for decontamination (see Centers for Disease Control and Prevention – public health guidance for community-level preparedness and response to severe acute respiratory syndrome [SARS]. Version 2. Available at: http://www.cdc.gov/ncidod/sars/guidance/I/pdf/healthcare.pdf).[46]

Disease containment is problematic. Virus was found in 97% of fecal samples from the Amoy Gardens outbreak, yet no rectal swabs were positive in hospital-acquired SARS cases in a Taiwan hospital. This was attributed to nosocomial respiratory spread.[48]

Preventing spread of SARS-CoV is made difficult by: (1) the potential spread by fomites, and conversion from droplet to airborne transmission[49]; (2) an incubation period averaging 6.4 days (usually 2–10 days; Hong Kong and Toronto 4.7 days,[50] but it may be as long as 16 days); (3) 3 to 5 days between disease onset and hospitalization; (4) the absence of specific symptoms; (5) often presenting as atypical (community-acquired) pneumonia[51]; (6) the lack of a reliable diagnostic test for early disease, putting HCWs at particular risk; (7) atypical presentations including diarrhea and bloody diarrhea without respiratory symptoms; and (8) early diagnosis depending solely on exposure to SARS or travel through epidemic or endemic areas.[3,5,52–55] This makes SARS-CoV an ideal agent for terrorists.

HUMAN EPIDEMIOLOGY

There were 2 major SARS outbreaks: (1) the early outbreak originating in Guangdong province in late 2002 (to early 2003); (2) isolated clusters in Taiwan, Singapore, and mainland China from the accidental release of the virus in 2003; and (3) a second outbreak beginning in late 2003 to early 2004, again reported from Guangdong province, in individuals with animal contacts with different SARS-CoV strains.[13] Molecular studies separated the human SARS-CoV isolated into early, middle, and late phase outbreak viruses. Human SARS-CoV isolates from 2003 to 2004 (sporadic cases from the same area of China) were more closely related to animal isolates than human isolates from 2002 to 2003 (the ''pandemic'' outbreak). This finding suggested ''an independent species-crossing'' event.[13]

Excluding ''superspreading events'' (SSEs), SARS-CoV has a calculated base-case reproduction number (R_0) of 2 to 4.[5] Attack rates range from 10.3% to 60%, with a risk of 2.4 to 31.3 cases/1000 exposure-hours.[3] SSEs include patients excreting high titers of virus, aerosol generation, contamination of the environment (fomites), and close contact in health care settings. These instances have resulted in as many as 300 infections from a single patient. SSEs have occurred in a hotel in Hong Kong, health care facilities in Hong Kong, Beijing, Singapore, and Toronto, and an air flight from Hong Kong to Beijing.[5,52]

In the Amoy Gardens high-rise apartments (Hong Kong), more than 300 residents developed SARS-CoV infections.[56] High concentrations of SARS-CoV were found in indoor aerosols originating from the plumbing in the building. Virus can survive 14 days in sewage at 4°C, and 2 days at 20°C.[57] The aerosols entered the apartments through bathroom drains, infecting the inhabitants, and were subsequently blown by prevailing winds and contaminated other buildings.[56,58] Meteorologic factors (ambient winds, low mixing heights preventing dispersion of aerosols, and a decrease in temperature enabling the virus to survive for longer periods) are believed to have

played a crucial role in the outbreak.[1,59] A positive association (although not cause and effect) between air pollution and SARS case-fatality rates exists.[60,61]

Nasopharyngeal swab SARS-CoV concentrations were directly related to the distance from the index case. Individuals (45% of patients) in adjacent units on the same block (Amoy Gardens Block E) as the index case had higher viral concentrations than those living further away (55% of patients living within 6 blocks), suggesting airborne spread.[56,62] The possibility of rodents and fomites playing a role could not be excluded.[62]

Other factors that contribute to nosocomial contagion include: (1) 1 m or less between beds; (2) lack of hand-washing facilities; (3) lack of changing facilities for the staff; (4) resuscitation performed on the ward; (5) HCWs working while symptomatic; (6) patients requiring oxygen therapy; and (7) patients requiring positive airway pressure ventilation. Viral loads might be high and shedding prolonged in immunocompromised patients. In addition, airflows around oxygen masks disseminate potentially infectious particles up to 0.4 m.[5,63] Use of a closed oxygen delivery mask with a respiratory filter can prevent droplet dispersal without increased positive pressure or end-tidal CO_2.[64]

Recommendations for containing the spread of disease include: (1) hand washing; (2) appropriate well-fitted facemasks; (3) isolation (airborne precautions); and (4) quarantine of asymptomatic contacts, thus significantly decreasing the time from onset of disease to isolation.[5] The application of infection control procedures in Singapore resulted in a significant drop in the R_0 (week 1, $R_0 = 7$; week 2, $R_0 = 1.6$; after week 2, $R_0 < 1$).[5]

HCWs remained at significant risk after initiation of infection control precautions. In Toronto, risk factors included performance of high-risk patient care procedures, inconsistent use of personal protective equipment, fatigue, and lack of adequate training. In this group of HCWs, 47% wore jewelry, 27% ate meals on the unit where they worked, and only 60% received any formal training. All HCWs interviewed indicated that they visited at least once the room of a patient with SARS who was not wearing a mask. Masks were not fit-tested until late in the outbreak. Forty percent reused items (stethoscopes, goggles, and cleaning equipment) elsewhere on the ward, and about one-third of HCWs assisted in endotracheal intubation of a patient with SARS.[65] There is evidence that SARS-CoV was transmitted to HCWs during cardiopulmonary resuscitation.[66]

Simulations based on stochastic susceptible-infected-recovered dynamics of hospital social networks predict that HCWs, particularly physicians, are the principle vector of disease. This model suggests that control of outbreaks could be achieved more effectively by (1) restricting physician visits to different hospital units (wards) and (2) vaccinating physicians and individuals with widespread contacts as a priority (when a vaccine becomes available).[67]

Another study screened asymptomatic HCWs' nasopharyngeal swabs with a more sensitive second-nested RT-PCR. This test can detect less than 800 copies of RNA/mm^3. These individuals were considered "first line...well protected" HCWs caring for patients infected with SARS-CoV. They all employed gloves, gowns, goggles, and N-95 masks. Second-nested RT-PCR assays (for SARS-CoV) were positive in 11.5% of these HCWs. No asymptomatic HCW became seropositive despite being RT-PCR positive. Those HCWs with positive second-nested RT-PCR were either required to stay at home or in central accommodation for 3 days before follow-up testing. Second and third tests were always negative. These investigators additionally recommended addition of regular nasopharyngeal swab screening to daily recording of temperature for all first-line HCWs.[7]

In Toronto, there were 358 cases, 2132 investigations, and 23,103 contacts that required health department attention. Only 13,291 of the contacts complied with quarantine recommendations, 8058 were not contacted until after the quarantine period, and 1754 could not be contacted. SARS-CoV transmission was limited to nosocomial and household spread. Health departments should expect to quarantine 100 contacts and investigate 8 possible cases for each case of SARS that meets the epidemiologic criteria.[50]

CLINICAL PRESENTATIONS

The WHO case definition for probable SARS includes: (1) fever greater than 38°C or history of fever in the preceding 48 hours; (2) new infiltrates on chest radiograph consistent with pneumonia; (3) chills or cough or malaise or myalgia or history of exposure; and (4) 1 or more positive tests for SARS-CoV.[4] Statistical analysis using "frequentistic" and Bayesian approaches when applied to SARS show that border (ie, airport) entry screening with a diagnostic test is rarely an efficacious method for preventing importation of a disease into a country.[68] Resources should be placed at entry points into the health care system and not international borders.[53]

Most patients present with flulike symptoms (fever, chills, cough, and malaise). Most patients (70%) develop dyspnea, and recurrent or persistent fever. Thirty percent significantly improve within 1 week. Mortality is 6.8% in patients less than 60 years old, and 43% in older patients. Male sex and comorbid conditions (eg, diabetes, hyperglycemia independent of diabetes, chronic hepatitis) increase mortality.[30,54,69] Overall, patients with and without comorbid conditions have 46% and 10% mortality, respectively.[30] Advanced age, high admission neutrophil count, and initial elevated lactic dehydrogenase (LDH) are independent correlates of an adverse outcome.[54]

During the first week (March 6–16th) of the 2003 Hong Kong SARS epidemic, there was an outbreak of human metapneumovirus (hMPV). hMPV RNA was detected in 20% of nasopharyngeal aspirates of SARS patients. HCWs and epidemiologic association with the SARS unit were risk factors for the hMPV infection. Coinfected patients had more cough (22.6%) and coryza (15.9%), but this was not statistically significant. Severity of illness and outcomes did not differ among those solely infected with SARS-CoV and those infected with both viruses.[70]

Table 1 enumerates clinical presentations.[3,4,7,32,48,51,52,71–75]

Table 2 describes the laboratory findings.[4,51,74,76,77]

Watery diarrhea is part of the initial presentation in approximately 20% of patients. In the outbreak at Amoy Gardens, Hong Kong, 73% of patients developed diarrhea with positive RT-PCR for SARS-CoV in 97% of their stool samples.[48,71] Cumulatively, 38.4% of patients develop a self-limited watery diarrhea (mean: 3.7 ± 2.7 days' duration) some time during their illness.[32,71] In HCWs who were believed to have acquired SARS by the respiratory route, 18.8% to 19.6% developed diarrhea. In 1 study, none of the HCWs had positive rectal swabs for SARS-CoV (by RT-PCR).[48]

Some contacts of SARS patients have been asymptomatically infected.[78] The most frequent symptom is fever higher than 38°C for more than 24 hours. Other symptoms vary and are nonspecific. They include sore throat, myalgia, and nausea. In up to 21% of patients, the initial chest radiographs may be normal.[77]

Pregnancy

Infants born to pregnant women with SARS did not seem to acquire the infection by vertical transmission.[79] In 1 study, there were 3 deaths among 12 pregnant women (25% mortality). In another study, 4 of 10 patients required intubation compared

Table 1
SARS-CoV infection signs and symptoms in patients at presentation

Signs and Symptoms	Frequency (Results Reported from Multiple Centers)	
	Adult Cases	Pediatric Cases (5.5 Months to 18 Years)
Asymptomatic viral colonization	11.5% of "well protected" first-line HCWs who did not seroconvert or later develop disease	
Fever	99%–100%	98%–100%
Chills or rigors	55%–90%	14.5% (rigor: 8.1%)
Cough (productive/nonproductive)	43%–100%	60%–62.9%
Shortness of breath	10%–80%	
Myalgia	20–60.9%	17.7%
Malaise/lethargy	35%–70%	6.5%
Headache	11%–70%	11.3%
Sputum production	10%–29%	
Sore throat	23.2%–30%	9.7% (independent predictor of severe disease)
Coryza	22.5% (not reported in all studies)	22.6%
Nausea or vomiting	10%–19.6%	41%
Diarrhea	11%–15% Fever and diarrhea, sometimes bloody diarrhea without respiratory symptoms at presentation.[46] Other studies have found 20.3% have watery diarrhea on presentation and 38.4% develop a self-limited diarrhea (most frequently in the first week) some time during the illness.[30] In the community outbreak in Amoy Gardens, Hong Kong, 73% of 75 patients had watery diarrhea and 97% had positive stools.[65,73] Hospital-acquired SARS less frequently presents with diarrhea (18.8%)[73]	

Data from Refs.[3,4,7,32,48,51,52,71–75]

with 12.5% of nonpregnant patients.[80] Four of 7 patients (57%) in the first trimester had spontaneous miscarriages, and 4 or 5 patients who became ill after 24 weeks' gestation delivered prematurely. Two pregnant women recovered and carried their babies to term, but the pregnancies were complicated by intrauterine growth restriction. No newborn presented with clinical SARS or had evidence of SARS-CoV infection (examining cord blood, placenta, and follow-up neonatal serology).[81]

Table 2
SARS-CoV infection: radiologic and laboratory findings in adult patients at presentation

Radiologic and Laboratory Findings	Frequency
Abnormal chest radiograph	78.3%–100% (One report: 35.5% of children have normal chest radiographs at presentation. Another report indicates 97% of children had abnormal chest radiographs)
Of those with abnormal chest radiographs	
Unilateral focal disease	56.4%
Progressive disease	90%
Detection of infiltrates by CT scan of:	
87% positive chest radiograph:	13% detected by chest CT scan
96% positive chest radiographs:	4% detected by chest CT scan
Anemia	Decrease in hemoglobin by 2 g/dL: 49% Hemolysis: 76%
Lymphopenia	69.6%–90% Wong et al[71] reported 98% developed lymphopenia (absolute counts <1000/mm³)
CD4 and CD8 lymphocyte counts	Decreases during the early course of disease. Low CD4 and CD8 counts at presentation a poor prognostic sign (associated with admission to the ICU or death)
Leukopenia	22–34.1% Wong et al[71] documented transient leukopenia in 64% of patients during the first week (WBC <4.0 × 10⁶/dL). 2.5% developed transient neutropenia (absolute count <0.5 × 10⁶/dL)
Leukocytosis	61% of patients in second and third week of illness (WBC >11.0 × 10⁶/dL).[30] Elevated absolute neutrophil count an independent predictor of an adverse outcome.
Thrombocytopenia	33%–44% (1 study reported thrombocytopenia to be mild and self-limited: platelet counts <40,000/mm³). 2.5% with platelet counts <50,000/mm³[71]
Hyponatremia	20.3%–60%
Hypokalemia	25.2%–47%
Hypocalcemia	60%
Increased ALT	23.4%–56%
Increased LDH	47%–87% High peak LDH independent predictor of an adverse outcome
Increased CPK	19%–56%
Prolonged activated partial thromboplastin time	18%–42.8%
Increased D-dimer	45% (reported from 1 center)

Data from Refs.[4,51,74,76,77]

Neonatal Disease

Of the 5 infants born to mothers with SARS, no infant had laboratory or clinical evidence of infection. Four of the 5 infants were born prematurely (28 weeks, 26 weeks, 32 weeks, 33 weeks, and 37 weeks). One infant developed necrotizing enterocolitis and ileal perforation, and another developed a perforation of the jejunum. The mother of the infant with necrotizing enterocolitis died 14 days after delivery.[82]

Pediatric Disease

Between February and June 2003, an outbreak of SARS occurred in Toronto, Canada. Children with potential exposure to SARS were classified as suspect SARS if they developed symptoms within 10 days of exposure, and probable SARS if the chest radiograph revealed lower respiratory tract disease.

Clinical disease manifestations included the following: fever higher than 38°C (70% of probable and 100% of suspect); respiratory symptoms (80% of probable and 60% of suspect); and headache, lethargy, vomiting, and diarrhea in a minority of patients. No children exhibited irritability or myalgia. Focal minor alveolar infiltrates were seen in 8 of 10 probable cases, and single cases of progressive lower lobe infiltrates, and perihilar peribronchial thickening. The patient with the bilateral infiltrates, a 17-year-old girl, developed respiratory distress and required supplemental oxygen. Nine children received intravenous ribavirin and 1 child received intravenous and aerosolized ribavirin. The clinical course for most children was described as "mild and brief."[1] There is only 1 published report of transmission of SARS-CoV from a pediatric patient with SARS.[73] In some children, exercise impairment and radiologic abnormalities persisted 6 months after diagnosis.[83] Thin-section computed tomography (CT) abnormalities have persisted in 32% of children up to 12 months after diagnosis, but were most often minor.[84]

The most common laboratory finding was lymphopenia. Some, but not all children exhibited neutropenia, mild thrombocytopenia, elevated liver enzymes (aspartate transaminase, alanine transaminase [ALT], and LDH), and elevated creatine phosphokinase (CPK) (1 case).[1]

Two to 3 months after the onset of illness, ~40% of children reported a self-limited thinning and shedding of hair (telogen effluvium).[75]

Patients on Dialysis

Patients on dialysis have a higher risk for acquiring SARS. They display the same typical symptoms (fever, myalgia, chills, rigors, gastrointestinal symptoms), but these are less severe. Although these patients sought medical attention at later stages of disease, the changes in their chest radiographs tended to be less severe than in patients not on dialysis (17% vs 45% with bilateral or multifocal changes). Patients on dialysis shed virus for longer periods, have greater transfusion requirements, require longer hospitalization, but have similar mortality compared with the control group.[85]

Mild or Subclinical Disease

In 1 study, 6 of 910 patients suspected of SARS-CoV infection and managed as outpatients had serologic evidence of infection. Five patients had normal chest radiographs and 2 patients had no symptoms. Those with symptoms complained of myalgia, fever, cough, and chills. However, more than half of these patients did not have follow-up serology.

Serologic testing of asymptomatic close contacts (1068 individuals) found 2 (0.19%) with IgG SARS-CoV antibodies. None of 29 household contacts of 13 SARS patients showed serologic evidence of infection. In another study, 1 symptomatic household contact was identified, but that individual had traveled to a SARS-"endemic" area. The investigators conclude that few individuals have mild or subclinical disease.[86–89]

COMPLICATIONS

HLA-B* 4601 haplotype (Taiwanese patients), HLA-B*0703 and HLA-DRB1*0301 (Hong Kong Chinese patients) alleles, low or deficient mannose binding lectin serum levels, and increased expression of the IP-10 gene (increased IP-10 concentrations) seem to be risk factors for SARS.[30,90] Liver/lymph node specific intercellular adhesion molecule 3 (ICAM3)-grabbing nonintegrin homozygotic individuals (L-SIGN or *CLEC4M*) have a lower risk.[30,91] In Hong Kong Chinese patients, interferon gamma (IFN-γ) +874 AA and IFN-γ AT genotypes were associated with a 5.19- and 2.57-fold increased risk of developing SARS.[91] Excessive induction of proinflammatory cytokines and chemokines, and recruitment of immune cells are postulated as the mechanisms for the most serious lung injury.[30,90]

Respiratory Complications

Patients discharged after SARS-CoV infection frequently have abnormal chest radiographs (15 of 24 patients). These abnormalities include patchy opacification, and volume loss. Abnormalities persisted in 15 of 25 patients 18 days after discharge. Opacifications and volume loss remained unchanged in 5 patients. CT studies of these patients revealed that 62% developed pulmonary fibrosis. Those who developed CT evidence of pulmonary fibrosis were older (mean age 45 vs 30.3 years), men (8:7 male/female ratio), were more often admitted to the intensive care unit (ICU) (26.6% vs 11.1%), had higher peak LDH levels (438.9 U/L vs 355.6 U/L), more often required pulsed steroid therapy, had more radiographic opacification, and more abnormal segments on thin-section CT.[92]

CT findings (at ~52 ± 20 days) revealed air trapping (92%), ground glass opacities (90%), reticulation (70%), parenchymal bands (55%), bronchiectasis (18%), consolidation (10%), and honeycombing (8%). A second CT (at ~141 ± 27 days) demonstrated resolution of ground glass and interstitial opacities, but air trapping persisted.[93]

The incidence of spontaneous pneumothorax (in nonventilated patients) is 1.7%. In half of these patients, the pneumothorax was bilateral. In 1 study, all patients had higher LDH levels, and all had received steroids.[94] In patients receiving mechanical ventilation, 14% developed pneumomediastinum with subcutaneous emphysema, and 24% developed a pneumothorax.[9]

Cardiovascular Complications

Cardiovascular complications were seen in most patients. Overall, 50.4% of the patients became hypotensive (28.1% in week 1; 21.5% in week 2; and, 14.8% in week 3). Tachycardia that could not be explained because of either fever or hypotension was present in 71.9% of patients (62.8% in week 1; 45.4% in week 2; and, 35.5% in week 3). Tachycardia was weakly associated with steroid therapy during the second and third weeks of illness, and persisted at follow-up in 38.8% of patients. Transient bradycardia was seen in 14.9% of patients. Reversible cardiomegaly without heart failure occurred in 10.7% of patients. Transient atrial fibrillation was seen in 1 patient.[95]

ARF

ARF occurred in 17% of patients admitted with probable SARS.[96] Most of the patients were men (77%), older, and more often had underlying illnesses (diabetes: 38% vs 6%, $P<.01$; and, heart failure: 38% vs 2%, $P<.001$). There was an increased incidence of respiratory failure (85% vs 26%, $P<.001$) and death (77% vs 8%, $P<.001$).[96]

In patients who initially had normal serum creatinines, the incidence of ARF was 6.7%, occurring 5 to 48 days into their illness (median 20 days). In this study, 91.7% of the patients died (vs 8.8% of patients without ARF: $P<.0001$).[33]

Complicating the ARF were hypotension (77%) from sepsis, gastrointestinal bleed, ARDS, and rhabdomyolysis (10%–43%).[96,97] In 1 study, 2 of the 3 patients with rhabdomyolysis died with multiple organ failure.[97]

Osteonecrosis

Joint pain is a common complaint after SARS-CoV infection. Osteonecrosis of the hip and knee is a risk for patients receiving steroid therapy. The risk for this complication for low total dose steroid therapy was 0.6%. For higher total dose steroid therapy and for therapy for more than 18 days, the risk is 9.9% to 13%.[98,99] Tumor necrosis factor α polymorphisms of promoter region (1031CT/CC and -863 AC genotypes) are not associated with susceptibility to SARS-CoV infection or the risk of interstitial lung fibrosis, but do represent risk factors for femoral head necrosis.[100] Bone density is reduced in patients receiving steroid therapy.[101] Bone resorption and formation biochemical tests cannot predict the development of this complication.[99]

Bacterial and Fungal Superinfection

Bacterial and fungal superinfection, related to prolonged duration of illness, prolonged ventilator support, and high-dose steroid therapy have been reported. These infections include *Aspergillus* species, *Mucor* species, *Pseudomonas aeruginosa*, *Klebsiella* species, methicillin-resistant *Staphylococcus aureus*, α-hemolytic *Streptococcus* species, and cytomegalovirus.[30]

Endocrine

Hypocortisolism is found in 39.3% of survivors of SARS-CoV infection. A few patients (3.3%) with hypocortisolism had transient subclinical thyrotoxicosis. Almost 7% were biochemically either centrally or primarily hypothyroid. Most hypothalamic-pituitary-adrenal axis abnormalities returned to normal within 1 year.[102]

Hepatitis

Reactive hepatitis is a common finding in 24% of patients having elevated ALT on admission, and up to 69% developing ALT elevation during the course of their illness. Concomitant hepatitis B was not associated with an adverse clinical outcome, but severe hepatitis was.[103] Liver damage seems to be directly caused by SARS-CoV rather than hypoxia.[104]

Psychiatric Complications

Psychiatric complications that significantly and negatively affected the quality of life have been seen in other survivors of ARDS. After intensive care treatment, 17% to 43% of patients suffered at least once from clinically significant psychiatric symptoms (point prevalence). Posttraumatic stress disorder (PTSD) was diagnosed in 21% to 35% of patients, and nonspecific anxiety in 23% to 48% of patients. Prevalence of PTSD at hospital discharge, and 5 and 8 years later, were 44%, 25%, and 24%,

respectively. PTSD and depression were associated with longer length of stay in the ICU and longer duration of mechanical ventilation and sedation.[105]

PTSD was diagnosed in Toronto residents who were quarantined in 28.9% of respondents to a voluntary survey. The presence of PTSD correlated with depressive symptoms (31.2%) and duration of quarantine.[106]

HCWs were more likely to suffer from PTSD if there was: (1) a perception of risk to themselves; (2) a significant impact on their work routines; (3) a depressive affect; and (4) assignment to a high-risk unit. HCWs caring for more than 1 patient with SARS experienced less PTSD.[107]

RADIOLOGY

Approximately one-fifth of patients presented with a normal chest radiograph, but developed infiltrates within 7 days (median 3 days) of onset of fever.[77] Of the 78.3% who presented with opacities on the chest radiographs, 54.6% were unilateral and the remainder were bilateral. The mean parenchymal involvement was 5% (range 1%–63% opacification). Radiographic changes appeared to peak at 8.6 days, which corresponded approximately to the initial treatment with steroids.[77]

The involvement of more than 1 lung zone and bilateral versus unilateral disease were associated with a higher risk of ICU admission and death.[77] Patients who died were older (56.9 $\pm$ 17.2 years vs 40.4 $\pm$ 16.6 years, P = .002), and had a higher frequency of comorbid conditions.[108] Abnormalities on thin-section CT in adults improved with time. Extent and persistence of the findings correlated with advanced age, severity of the disease, and diffusion capacity adjusted for hemoglobin.[109]

In children, SARS cannot be distinguished from other forms of viral pneumonia.[110] One report indicates that 35% of children present with normal chest radiographs. The most common chest radiograph finding was consolidation (45.2%), sometimes with peripheral multifocal disease (22.6%), peribronchial thickening (14.5%), and rarely pleural effusion. Interstitial disease was not observed. In another report, 97% of cases had abnormal chest radiographs.[72,73]

LABORATORY TESTING

Sensitivity of RT-PCR collected in the first 3 days of the illness is inadequate. The 6-item clinical score for emergency room triage during a SARS outbreak of febrile patients, most of whom were otherwise healthy, seems to be 92.6% sensitive and 71.2% specific. These figures were generated in a noninfluenza season.[5] A promising RT-PCR is under development to detect viremic blood donor samples early in the symptomatic disease.[111]

Confirmation of infection is made by identifying the SARS-CoV nucleocapsid (N) protein in the serum by N antigen-capture enzyme-linked immunosorbent assay (ELISA) and N antigen-capture chemiluminescent immunoassay. Serology can be accomplished by commercially available indirect ELISA kit, and indirect immunofluorescent assay (IFA).[78] ELISA and IFA results nearly always tend to be in agreement. Serology is positive in 8.3% of patients in the first 2 weeks. Paired serology was positive in 96.2% of patients in whom RT-PCR was positive in 64% of the same patients.[112] SARS-CoV patients' serums falsely cross-react by ELISA and Western blot for human T-lymphotropic virus (HTLV-1 and HTLV-II).[113]

Viral cultures are performed in African green monkey Vero E6 cell monolayers. Confirmation is by RT-PCR.[114] RNA amplification by real-time nucleic acid sequence-based amplification seems to be at least as sensitive as RT-PCR.[115]

During the first 2 weeks of illness, RT-PCR has a diagnostic yield for tracheal aspirates of 66.7%, and 56.5% for stool.[114] Pooled throat and nasal swabs, rectal swab, nasal swab, throat swab, and nasopharyngeal aspirate had yields from 29.7% to 40% for the first 2 weeks of illness. Throat washing and urine had lower yields (17.3% and 4.5%, respectively). Viral cultures had lower yields, and no specimens were positive by culture that were negative by RT-PCR.[114]

In the first 4 to 5 days of illness, it seems that nasopharyngeal aspirates and throat swabs are more useful in detecting virus, whereas stool specimens are more valuable after 5 days of illness (20% sensitivity). Urine samples are of little or no use. Clinical specimens remain stable at 4°C or −70°C for weeks and may be stored for later testing.[116]

RT-PCR can detect SARS-CoV after 30 days in respiratory secretions, stool, and urine in some patients, but virus cannot be isolated by culture after 3 weeks.[116] Quantitative RT-PCR (RTq-PCR) used to measure the viral load in nasopharyngeal aspirates (obtained from day 10–15 after the onset of symptoms) correlated with oxygen desaturation, the need for mechanical ventilation, diarrhea, abnormal liver function studies, and death. Serum RTq-PCR is predictive of oxygen desaturation, the need for mechanical ventilation, and death. Stool viral load is associated with diarrhea, and urine viral load correlates with abnormal urine analysis.[117]

Nasopharyngeal viral loads tend to peak at day 10 and decrease to less than initial levels by day 15. It seems, however, that the worsening of the clinical condition in week 2 is not directly related to viral replication but more to the immunopathology of the infection.[71] The applications of surface-enhanced laser desorption/ionization (SELDI) ProteinChip technology producing proteomic fingerprints examined more than 800 common proteomic features. SELDI found that 95% of SARS patients had similar serum proteomic profiles. For specific proteomic features, sensitivity and specificity ranged from 95% to 97% and 97% to 100%, respectively. Combining all the biomarkers produced a SARS-specific fingerprint. Immunoglobulin κ light chain presence correlated with SARS-CoV viral load and seems to be helpful in diagnosing the infection.[118] Serum amyloid protein levels detected by SELDI, peptide mapping, and tandem mass spectrometric analysis correlated with the extent of pneumonia on serial chest radiographs.[119]

Monoclonal antibody has been used to identify viral infection by immunofluorescence staining, Western blot, or immunohistology.[120]

Immune Response

Antibodies develop late in the first week after the onset of symptoms. Specific IgG antibodies (seroconversion) are found in more than 95% of patients by day 25. CD4$^+$ and CD8$^+$ cells are stimulated to produce antibody and kill infected cells, respectively. Proinflammatory cytokines released by activated macrophages are believed to contribute to local inflammation and contribute to SARS pathology.[121]

Laboratory and Autopsy

All specimens from suspected SARS patients must be handled using biosafety laboratory level 3 (BSL-3) practices in a BSL-2 facility. These specimens should be stored in a secure place using BSL-3 precautions with strict access control, inventorying of specimens, and the inventory audited at frequent intervals. Unneeded specimens should be sterilized and discarded according to BSL-3 protocols. All personnel should be appropriately trained for BSL-3 precautions, retrained at designated intervals, drills conducted, and laboratory procedures audited on a regular basis.[47]

In community hospitals, generally the acid-fast bacilli room, a closed separate negative-pressure room with a biologic safety hood vented through a high efficiency particulate air (HEPA) filter may be adapted for handling these specimens. Viral isolation and cultures must never be attempted in these facilities, and are permitted only in a BSL-3 facility.

Postmortem examinations on SARS patients should be undertaken only in a specially designed BSL-3 laboratory. This facility should be physically separated from the rest of the health care facility; it should be divided into 5 sections (a clean area, a semi-contaminated area, a contaminated area, and 2 buffer zones); it should be 2 ventilation systems separate from the remainder of the building; laminar flow should be from clean areas to progressively contaminated areas; negative pressures should be from clean, semi-contaminated to contaminated areas with pressure gradients; and there should be no tap water or sewage system. Use of personal protective equipment must be strictly adhered to. The mortuary must be adjacent to the buffer zone next to the contaminated (autopsy) room, and a downdraft table ventilation system with HEPA filtration must be employed.[122] Details are described in Ref.[122] and in Refs.[2–5] therein.

DIFFERENTIAL DIAGNOSIS

Bacterial community-acquired pneumonias that may result in ARDS and mistaken for SARS-CoV infection include *Streptococcus pneumonia*, *Haemophilus influenzae*, *Moraxella catarrhalis*, community-associated methicillin-resistant *Staphylococcus aureus*, and atypical pneumonias (eg, *Legionella* species).[55] The differential diagnosis of viruses that commonly cause ARDS with fever includes seasonal influenza (A or B), parainfluenza virus, avian influenza, respiratory syncytial virus, adenovirus, varicella, hMPV, and hantavirus.[55,123] Other organisms likely to require "mass" critical care, have the potential to spread disease to HCWs, and result in an extensive community epidemic with high morbidity and mortality are smallpox, viral hemorrhagic fever, plague, tularemia, and anthrax.[55]

TREATMENT AND PREVENTION

> Eye of newt, and toe of frog,
> Wool of bat, and tongue of dog,
> Adder's fork, and blind-worm's sting,
> Lizard's leg, and howlet's wing,–
> For a charm of powerful trouble,
> Like a hell-broth boil and bubble.
> William Shakespeare, Macbeth

Aerosolized SARS-CoV viral droplets are 0.1 to 0.2 μm (as opposed to the 4- to 8-μm droplets produced by coughing, sneezing or talking). SARS-CoV remains viable for several days at normal ambient room temperatures and humidity. Suspect patients must be immediately isolated using contact, droplet, and airborne isolation precautions in a negative-pressure single room.[55,124] In 1 study, no virus was detected in the air from the negative-pressure room of a patient on mechanical ventilation (with a 0.023-μm filter on the exhalation circuit) before and after extubation.[124] Viral inactivating methods and agents are listed in **Table 3**.[43–46]

Immunity to SARS-CoV has been achieved in animal models by the induction of neutralizing antibodies using live-attenuated vaccinia virus Ankara expressing S glycoprotein vaccine, recombinant spike protein polypeptide vaccine (generated in

Table 3
SARS-CoV stability and inactivating agents

Agent or Activity	Comments
Povidone-iodine	2-minute treatment reduced infectivity to less than detectable levels
70% ethanol	Equivalent to povidone-iodine
Formalin Glutaraldehyde Methanol Acetone	Fixation of Vero E6 SARS-CoV for 5 minutes with these agents eliminated all infectivity
Heating at 56°C for 60 minutes in absence of protein	Eliminates infectivity
Solvent/detergents	For virus inactivation: Triton X-100 required 2 hours; Tween 80 required 4 hours; and sodium cholate required up to 24 hours
Octanoic acid	Does not inactivate virus
Heating at 56°C for 60 minutes in the presence of 20% protein	Residual infectivity remains
Heating at 60°C for at least 30 minutes in the presence of protein	Minimal requirement to eliminate infectivity in the presence of protein
Ultraviolet subtype C	Inactivated virus in 40 minutes. The presence of bovine serum albumin limited ability to inactivate virus
Ultraviolet A light	Requires the addition of psoralen to enhance inactivation of virus. The presence of bovine serum albumin limited ability to inactivate virus
Virus in suspension	Maintains infectivity for 9 days
Dried virus	Maintains infectivity for 6 days
Virus in fomites and stool	Maintains infectivity 24–72 hours

Data from Refs.[43–46]

Escherichia coli with spike polypeptide DNA), adenoviral-based (expressing either N or S proteins) virus, recombinant baculovirus, Newcastle disease virus, attenuated vesicular stomatitis virus expressing S protein, attenuated *Salmonella enterica* serovar Typhi and serovar Typhimurium, S protein on *Lactobacillus casei*, rhabdovirus-based vaccines, attenuated parainfluenza virus expressing S protein, and inactivated SARS-CoV vaccine, among others.[6,21,125–137] Comprehensive reviews of vaccine development are referenced.[2,21]

Human monoclonal antibody (hmAbs) 80 R directed against the SARS-CoV S protein, acting as a viral entry inhibitor by blocking its binding to the ACE-2 receptor, protects mice against infection.[138] ACE-2 itself protects murine lungs from acute lung injury, and SARS-spike protein-mediated lung injury.[139]

The SARS-CoV strain from the first outbreak (2002/early 2003) could be neutralized by the hmAbs 80R and S3.1. The SARS-CoV GD03 strain from the second SARS outbreak (2003/2004) was resistant to both these products. Two other hmAbs products (m396 and S230.15) were able to neutralize strain GD03, isolates from the first SARS outbreak (Urbani, Tor2), and isolates from palm civets.[140] The use of 2 noncompeting hmAbs may allow for the use of lower doses as the result of synergy, and prevent the emergence of resistant mutants.[141]

Conversely, antibodies that neutralize most (human) SARS-CoV S glycoproteins enhanced entry mediated by the civet virus S glycoprotein. This result occurs because of the antibody interaction with conformational epitopes in the human ACE-2 binding domain.[142]

Pathogen-free chickens immunized with inactivated SARS-CoV produced eggs from which anti-IgY (egg yolk) anti-SARS-CoV antibody was extracted. The product had a neutralization titer of 1:640. It could be lyophilized, reconstituted without loss of activity, and maintain good thermal stability.[143]

Other theoretic treatments include treatment of SARS ARDS by blocking the pulmonary renin-angiotensin system or treatment with ACE-2.[37,38]

Uncontrolled trials suggest that IFN alfacon-1 (a synthetic interferon) with steroids, protease inhibitors with ribavirin, or convalescent plasma with neutralizing antibody may be useful for treatment. Some investigators suggest considering prophylaxis with IFN or hyperimmune globulin for unprotected exposures.[42] A hybrid IFN (IFN-α B/D) and a mismatched double-stranded (ds) RNA IFN inducer (Ampligen [poly I: poly C124]), also display antiviral activity.[144]

Randomized controlled trials are not available to evaluate treatment regimens. Early positive outcomes using ribavirin and steroids led to widespread use of that combination. In 1 study of 71 cases (97% laboratory confirmed), antibiotics, ribavirin plus a 3-week step-down steroid therapy and pulsed methylprednisolone "rescue" resulted in 3.4% mortality, all in patients older than 65 years. Complications suffered by these patients included hyperglycemia (58%), pneumomediastinum (13%), psychiatric symptoms (7%), and ventilator associated pneumonia (2%).[145] Steroid therapy, including pulsed steroids, has been used in critically ill patients. High-dose and prolonged steroid therapy predisposed patients to multiple adverse outcomes, especially avascular necrosis (in 1 study, 12% of patients).[146]

Some reports demonstrate ribavirin antiviral activity and synergy with type I IFN (IFN-β1a or leukocytic IFN-α).[8] Subsequent reports indicated that ribavirin and mizoribine (both inosine-5' monophosphate dehydrogenase inhibitors) had poor in vitro antiviral activity and were associated with frequent toxicity.[146,147]

Concern exists about the adverse effects of ribavirin. These effects include dose-dependent anemia with doses 1.2 g/d or greater for more than 10 days (hemolysis or bone marrow suppression), arrhythmia, elevated lactate and pyruvate levels, hypocalcemia, and hypomagnesemia. Patients have complained of chest pain and dizziness. Less frequently, patients develop hyperuricemia, hyperbilirubinemia, interstitial pneumonia, leukopenia, and thrombocytopenia. Ribavirin therapy resulted in anemia in 72.7% of patients, with 50% decreasing more than 2 g/dL of hemoglobin. Hypoxemic and anemic patients receiving ribavirin had a higher mortality (29%).[148]

Indomethacin has significant in vitro anti-SARS-CoV activity.[149] Other antiinflammatory agents (chloroquine, amodiaquine, and pentoxifylline) were inactive in vitro.[144] Niclosamide and several interferons have demonstrated in vitro (in Vero E6 cells) activity.[150,151] Several nucleoside analogues, protease inhibitors, reverse transcriptase inhibitors, neuraminidase inhibitors, amantadine, and foscarnet did not adequately inhibit cytopathic effect.[151]

Ritonavir/lopinavir (Kaletra), the human immunodeficiency virus protease inhibitor combination (400 mg ritonavir and 100 mg lopinavir) has been suggested for the early treatment of SARS. IFN, although not recommended as standard therapy, possesses in vitro antiviral activity. Cases reported suggest that they should be subjected to clinical trial.[146,152] In 1 study, the combination of lopinavir/ritonavir and ribavirin resulted in a lower incidence of intubation with a matched cohort (0% vs 11%, respectively),[153] and ARDS or death (2.4%) versus historical control (28.8%, $P<.001$) at 3 weeks.[152]

Novel CoV-inhibiting agents that seem theoretically promising include carbohydrate-binding agents, nucleoside analogues with 6-chloropurine nucleobase, ranpirnase (onconase, an amphibian oocyte/early embryo ribonuclease), and drugs targeting viral envelope protein.[135,154,155] Safety testing of equine anti-SARS-CoV F(ab′)2 has been undertaken in macaques.[156] Patent applications for cathepsin L inhibitors (inhibitors of SARS-CoV entry into cells), SARS-CoV protease inhibitors, IFN, and short interfering RNAs that inhibit the expression of SARS-CoV genes, have either been made or are under consideration.[21,157] ACE-2 cellular receptor and the SARS-CoV spike protein are likewise therapeutic targets.[158]

A review in 2006 of SARS therapy administered during the epidemic found that finding clear-cut treatment benefits was elusive. There were 26 reports of inconclusive benefits and 4 reports of possible harm related to ribavirin therapy, 25 inconclusive reports and 4 reports of possible harm from steroid therapy, and inconclusive reports for lipinavir/ritonavir therapy (2), IFN-α therapy (3), and convalescent plasma or immunoglobulin therapy (7).[8]

Virus-encoded enzymes (3C-like cysteine protease and papainlike cysteine protease, nucleoside triphosphate hydrolase/helicase and RNA-dependent RNA polymerase) have been considered therapeutic targets. Other compounds exhibiting in vitro activity include valinomycin, glycopeptide antibiotics, plant lectins, hesperetin, glycyrrhizin, aurintricarboxylic acid, niclosamide, nelfinavir, and calpain inhibitors.[159]

SUMMARY

Once more unto the breach, dear friends, once more;
Or close the wall up with our English dead.
In peace there's nothing so becomes a man
As modest stillness and humility;
But when the blast of war blows in our ears,
Then imitate the action of the tiger:
Stiffen the sinews, summon up the blood.
William Shakespeare, Henry V

Identification of a possible SARS patient must be made on admission to the hospital. Symptoms almost if not always overlap common respiratory diseases present in the community, making the epidemiologic history critical. Rapid definitive laboratory testing of patients (and HCWs) must be available. Recognizing the patient as a risk for SARS becomes a difficult task if this is a result of a bioterrorist attack, and the patient is 1 of the first to present to the institution.

Placement of the patient in a negative-pressure room, strict enforcement of infection control measures, and the use of personal protective equipment are essential. The use of a closed oxygen delivery mask with a respiratory filter is mandatory in all patients requiring supplemental oxygen. Regular screening of HCWs for nasopharyngeal carriage may be necessary. In addition, the laboratory needs to be warned of the possibility of a SARS-CoV infection as soon as possible. The danger of nosocomial spread, HCW-, and laboratory-acquired infection is significant, even after implementation of infection control practices.

As shown by the Amoy Gardens outbreak, SARS may represent an environmental hazard through contamination by viral aerosols associated with plumbing.

There are no definitive treatment modalities. Ribavirin and steroid therapy seems to be the most frequent choice of clinicians during the epidemics, yet there is a lack of clear evidence of benefit.

The horseshoe bat is the natural reservoir for the SARS-CoV, with civets as the amplification host, and "wet markets" and farms as the amplification centers.[16] SARS-CoV has significant similarities to avian CoVs and SARS-CoV-like viruses found in mammals (masked palm civets and racoon dogs) from the Chinese live-animal markets. The 5′ polymerase gene is of mammalian origin, whereas the 3′ end structural gene excluding the S glycoprotein is of avian origin. The S glycoprotein is of feline and avian origin. The SARS-CoV rapidly evolved from the group 2 CoVs. It still circulates in animal reservoirs, ready to reemerge and cause a new epidemic.[160,161]

Challenges faced by the health care institution include closure of the ICU beds, loss of staff through quarantine and illness, emergent introduction of new, complex, and restrictive infection control procedures, rapid staff education, system planning, and maintaining morale.[162] Booth and Stewart (Toronto)[162] indicate that coordinated leadership, communication infrastructure, and systems in place to quickly expand and modify critical care services is essential to meeting the demands of a SARS outbreak.

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