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Severe Acute Respiratory Syndrome and Coronavirus

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Severe acute respiratory syndrome (SARS) emerged unexpectedly in 2003 and posed an enormous threat to international health and economy.1–4 By the end of the epidemic in July 2003, 8098 probable cases were reported in 29 countries and regions with a mortality of 774 (9.6%).5 SARS re-emerged at small scales in late 2003 and early 2004 in South China after resumption of wild animal trading activities in markets.6,7

THE VIRUS AND ITS ORIGIN

Members of the Coronaviridae family are classified into 3 groups based on serologic and, more recently, genetic similarity. Coronaviruses (CoVs) are found in a wide range of animal species including cat, dog, pig, rabbit, cattle, mouse, rat, chicken, pheasant, turkey, whale, as well as humans. Before the SARS epidemic, the only recognized coronaviruses causing respiratory tract infection in humans were HCoV-OC43 and HCoV-229E. In 2003, a previously unrecognized CoV was detected from SARS patients,8–15 and was confirmed to be the causative agent for SARS; it became known as SARS-CoV. Retrospective serologic surveys suggested that cross-species transmission of SARS-CoV or its variants from various animal species to humans might have occurred frequently in the wet market, as a high seroprevalence was detected among animal handlers who had no notable SARS-like illnesses.16

The role of masked palm civets in transmitting SARS-CoV to humans was first suspected in 2003 when a closely related variant of SARS-CoV was detected from palm

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civets in Dongmen market, Shenzhen.\textsuperscript{17} Further epidemiologic evidence was obtained during a small-scale outbreak in late 2003 and early 2004, in which 3 of the 4 patients had direct or indirect contact with palm civets.\textsuperscript{6,18} Subsequent sequence analysis suggested that the SARS-CoV–like virus has not been circulating among market masked civets for a long period, and therefore the true natural reservoir for SARS-CoV was sought. In 2005, CoVs that are similar to SARS-CoV were found in horseshoe bats by 2 independent research teams.\textsuperscript{19,20} These bat SARS-like CoVs share 88\% to 92\% sequence homology with human or civet isolates, but with key differences found in the region encoding spike (S) protein that is critical in determining host range and tissue tropism.\textsuperscript{21} The data suggest that bats could be a natural reservoir of a close ancestor of SARS-CoV, and that the CoVs seem to have used an entirely new receptor when they crossed species from bats to palm civets and humans.

In addition to masked palm civets and bats, other animal species might have been involved in the evolution and emergence of SARS-CoV. At least 7 animal species can harbor SARS-CoV in certain circumstances, including raccoon dog, red fox, Chinese ferret, mink, pig, wild boar, and rice field rat.\textsuperscript{21}

**EPIDEMIOLOGY**

In November 2002, there was an unusual epidemic of severe pneumonia of unknown origin in Foshan, Guangdong Province in southern China, with a high rate of transmission to health care workers (HCWs).\textsuperscript{22,23} A retrospective analysis of 55 patients admitted to a chest hospital with atypical pneumonia in Guangzhou between January 24 and February 18 2003 showed positive SARS-CoV in the nasopharyngeal aspirates (NPA), whereas 48 (87\%) patients had positive antibodies to SARS-CoV in their convalescent sera. Genetic analysis showed that the SARS-CoV isolates from Guangzhou had the same origin as those in other countries, with a phylogenetic pathway that matched the spread of SARS to other parts of the world.\textsuperscript{24}

A 64-year-old physician from southern China, who had visited Hong Kong (HK) on 21 February 2003 and died 10 days later of severe pneumonia, was the source of infection causing subsequent outbreaks of SARS in HK and several other countries.\textsuperscript{1–3,25} At least 16 hotel guests or visitors were infected by the Guangdong physician while they were visiting friends or staying on the same floor of Hotel M, where the physician had stayed briefly. Through international air travel, these visitors spread the infection globally within a short period.

SARS seems to spread by close person-to-person contact via droplet transmission or fomite.\textsuperscript{26} The high infectivity of this viral illness is shown by the 138 patients (many of whom were HCWs) who were hospitalized with SARS within 2 weeks as a result of exposure to a single patient (a visitor to Hotel M), who was admitted with community-acquired pneumonia (CAP) to a general medical ward at the Prince of Wales Hospital (PWH) in HK.\textsuperscript{1,27} This super-spreading event was believed to be related to the use of a jet nebulizer, driven by air at 6 L/min, for the administration of aerosolized salbutamol to an index patient, together with overcrowding and poor ventilation in the hospital ward.\textsuperscript{1,26} SARS-CoV was also detected in respiratory secretions, feces, urine, and tears of infected individuals.\textsuperscript{28} In addition, there was evidence to suggest that SARS might have spread by airborne transmission in a major community outbreak at the Amoy Garden, a private residential complex in HK.\textsuperscript{29} Higher nasopharyngeal viral load was found in patients living in adjacent units of the same block inhabited by the index patient at the Amoy Garden, whereas a lower, but detectable, nasopharyngeal viral load was found in patients living further away from the index patient.\textsuperscript{30} Air samples obtained from a room occupied by a SARS patient and swab
samples taken from frequently touched surfaces in rooms and in a nurses’ station were positive by polymerase chain reaction (PCR) testing.\textsuperscript{31} The temporal-spatial spread of SARS among inpatients in the index medical ward of the PWH in HK was also consistent with airborne transmission.\textsuperscript{32} These data support SARS having the potential to be converted from droplet to airborne droplet transmission,\textsuperscript{27–32} and they emphasize the need for adequate respiratory protection in addition to strict contact and droplet precautions when managing SARS patients.

**CLINICAL FEATURES**

The estimated mean incubation period was 4.6 days (95% confidence interval [CI] 3.8–5.8 days), whereas the mean time from symptom onset to hospitalization varied between 2 and 8 days, decreasing in the course of the epidemic. The mean time from onset to death was 23.7 days (CI 22.0–25.3 days), whereas the mean time from onset to discharge was 26.5 days (CI 25.8–27.2 days).\textsuperscript{33} The major clinical features on presentation include persistent fever, chills/rigor, myalgia, dry cough, headache, malaise, and dyspnea. Sputum production, sore throat, coryza, nausea and vomiting, dizziness, and diarrhea are less common features (\textbf{Table 1}).\textsuperscript{1–4,34}

Watery diarrhea was a prominent extrapulmonary symptom in 40% to 70% of patients with SARS 1 week into the clinical course of the illness.\textsuperscript{35,36} Intestinal biopsy specimens taken by colonoscopy or autopsy revealed evidence of secretory diarrhea with minimal architectural disruption, but there was evidence of active viral replication within the small and large intestines.\textsuperscript{36} Reactive hepatitis was a common complication of SARS-CoV infection, with 24% and 69% of patients respectively having increased alanine aminotransferase (ALT) levels on admission and during the subsequent course of the illness. Those with severe hepatitis had worse clinical outcomes, but chronic hepatitis B itself was not associated with disease severity.\textsuperscript{37}

SARS-CoV was detected in the cerebrospinal fluid and serum samples of 2 cases with status epileptics.\textsuperscript{38,39} The data suggest that a severe acute neurologic syndrome might occasionally accompany SARS.

| Table 1 |
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| **Clinical features of SARS on presentation** |
| **Symptom** | **% of Patients with Symptom** |
| Persistent fever >38°C | 99–100 |
| Nonproductive cough | 57–75 |
| Myalgia | 45–61 |
| Chills/rigor | 15–73 |
| Headache | 20–56 |
| Dyspnea | 40–42 |
| Malaise | 31–45 |
| Nausea and vomiting | 20–35 |
| Diarrhea | 20–25 |
| Sore throat | 13–25 |
| Dizziness | 4.2–43 |
| Sputum production | 4.9–29 |
| Rhinorrhea | 2.1–23 |
| Arthralgia | 10.4 |

\textit{Data from} Refs.\textsuperscript{1–4,25}
Older subjects might have atypical presentation such as decrease in general well-being, poor feeding, fall/fracture, and, in some cases, delirium, without the typical febrile response (temperature >38°C). In contrast, young children (<12 years of age) often ran a more benign clinical course mimicking other viral upper respiratory tract infections, whereas teenagers tended to have a clinical course similar to that of adults. There was no reported fatality in young children and teenage patients, but SARS in pregnancy carried a significant risk of mortality. Orchitis was reported as a complication in male patients. A meta-analysis showed overall seroprevalence rates of 0.1% for the general population and 0.23% for HCWs, although the true incidence of asymptomatic infection remains unknown.

A case-control study involving 124 medical wards in 26 hospitals in Guangzhou and HK has identified 6 independent risk factors of super-spreading nosocomial outbreaks of SARS (Box 1): minimum distance between beds less than 1 m, performance of resuscitation, staff working while experiencing symptoms, SARS patients requiring oxygen therapy or noninvasive positive pressure ventilation (NPPV), whereas availability of washing or changing facilities for staff was a protective factor. Experimental studies have shown that the exhaled air particle dispersion distances from patients receiving oxygen via a simple oxygen mask and a jet nebulizer were 0.4 m and at least 0.8 m, respectively. Exhaled air distances from NPPV via the different face masks could range from 0.4 m to 1 m, with more diffuse room contamination for face masks that require connection to the whisper swivel exhalation device. These data have important clinical implications in preventing any future nosocomial outbreaks of SARS and other respiratory infections. HCWs should take adequate respiratory precautions when managing patients with CAP of unknown cause that is complicated by respiratory failure within these distances.

The clinical course of SARS generally followed a typical pattern: phase I (viral replication) was associated with increasing viral load and was clinically characterized by fever, myalgia, and other systemic symptoms that generally improved after a few days; phase II (immunopathologic injury) was characterized by recurrence of fever, hypoxemia, and radiological progression of pneumonia with reductions in viral load. The high morbidity of SARS was highlighted by the observation that, even when there was only 12% of total lung field involved by consolidation on chest radiographs, 50% of patients would require supplemental oxygen to maintain satisfactory oxygenation greater than 90%, whereas about 20% of patients would progress into acute respiratory distress syndrome (ARDS) necessitating invasive ventilatory support. Peiris and colleagues showed a progressive decrease in rates of viral shedding from

| Box 1 |
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| Independent risk factors of super-spreading nosocomial outbreaks of SARS |
| Minimum distance between beds <1 m (odds ratio [OR] 6.98, 95% CI 1.68–28.75, P = .008) |
| Washing or changing facilities for staff (OR 0.12, 95% CI 0.02–0.97, P = .05) |
| Performance of resuscitation (OR 3.81, 95% CI 1.04–13.87, P = .04) |
| Staff working while experiencing symptoms (OR 10.55, 95% CI 2.28–48.87, P = .003) |
| SARS patients requiring oxygen therapy (OR 4.30, 95% CI 1.00–18.43, P = .05) |
| SARS patients requiring NPPV (OR 11.82, 95% CI 1.97–70.80, P = .007) |

Data from Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? Clin Infect Dis 2007;44:1017–25.
nasopharynx, stool, and urine from day 10 to day 21 after symptom onset in 20 patients who had serial measurements with reverse transcriptase (RT)-PCR. Thus, clinical worsening during phase II was most likely the result of immune-mediated lung injury as a result of an overexuberant host response and could not be explained by uncontrolled viral replication.35

**LABORATORY FEATURES**

Lymphopenia, low-grade disseminated intravascular coagulation (thrombocytopenia, prolonged activated partial thromboplastin time, increased D-dimer), increased lactate dehydrogenase (LDH), and creatinine phosphokinase (CPK) were common laboratory features of SARS.1–3,56,57 Absolute lymphopenia occurred in 98% of cases of SARS during the clinical course of the disease. The CD4 and CD8 T lymphocyte counts declined early in the course of SARS, whereas low counts of CD4 and CD8 at presentation were associated with adverse clinical outcome.58 The CD3 and CD4 T cell percentages were reported to be negatively correlated with the appearance of immunoglobulin G (IgG) antibody against SARS-CoV.59

A retrospective study in Toronto found that all laboratory variables except absolute neutrophil count (ANC) showed fair to poor discriminatory ability in distinguishing SARS from other causes of CAP, and that routine laboratory tests may not be reliable in the diagnosis of SARS.60 Nevertheless, when evaluating patients with CAP and no immediate alternative diagnosis who are epidemiologically at high risk, a low ANC on presentation, along with poor clinical and laboratory responses after 72 hours of antibiotic treatment, may raise the index of suspicion for SARS and indicate a need to perform SARS-CoV testing.61 Scoring systems may help identify patients who should receive more specific tests for influenza or SARS.62

**RADIOLOGICAL FEATURES**

Radiographic features of SARS generally resemble those found in other causes of CAP.63 The more distinctive radiographic features of SARS include the predominant involvement of lung periphery and the lower zone in addition to the absence of cavitation, hilar lymphadenopathy, or pleural effusion.1,63 Radiographic progression from unilateral focal air-space opacity to multifocal or bilateral involvement during the second phase of the disease, followed by radiographic improvement with treatment, is commonly observed.1,63 In a case series, 12% of patients developed spontaneous pneumomediastinum, and 20% of patients developed evidence of ARDS in a period of 3 weeks.35 The incidence of barotrauma (26%) in intensive care unit (ICU) admissions was high despite the application of low-volume and low-pressure mechanical ventilation.64 High-resolution computed tomography (HRCT) of thorax was useful in detecting lung opacities in cases with a high index of clinical suspicion of SARS but unremarkable chest radiographs. Common HRCT features included ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening, with predominantly a peripheral and lower lobe involvement (Fig. 1).65

**PATHOGENESIS**

The route of entry for SARS-CoV in humans is through the respiratory tract, mainly via droplet transmission. Although human intestinal cells have proven to be susceptible to SARS-CoV replication, the role of the intestinal tract as a portal of entry remains uncertain.66 Similarly, although infectious viruses were found in stool samples, there was
insufficient evidence to support the fecal-oral route of transmission for SARS-CoV infection.

The surface envelop S protein of SARS-CoV seems to play a key role in establishing infection and determining the cell and tissue tropism. The SARS-CoV S protein has 3 domains: the N-terminal half (S1) contains a receptor-binding domain (RBD), and the C-terminal half (S2) contains a fusion peptide. Entry of the virus requires receptor binding, followed by conformational change of the S protein, and then cathepsin L–mediated proteolysis within the endosome. The angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV, and is expressed on a wide variety of tissues including lungs, intestine, kidneys, and blood vessels. The presence of ACE2 seems not to be the sole determinant for tropism of SARS-CoV. For instance, SARS-CoV has been found in colonic enterocytes and hepatocytes that lack ACE2, whereas SARS-CoV has not been detected in endothelial cells of blood vessels and smooth muscle cells of intestine, despite their expression of ACE2.

There are some data to suggest that, in addition to ACE2, 2 other surface molecules play a critical role in establishing SARS-CoV infection in human cells. DC-SIGN (CD209) dendritic cell–specific intercellular adhesion molecule–grabbing nonintegrin, is a type 2 transmembrane adhesion molecule that recognizes a variety of microorganisms. DC-SIGN is expressed in macrophages and dendritic cells including those found in skin, lungs, intestine, rectum, cervix, placenta, and lymph node. However, the binding of SARS-CoV to DC-SIGN does not lead to entry of viruses into dendritic cells; instead it facilitates the transfer of viruses to other susceptible cells. In this way, the dendritic cells play an important role in virus dissemination within the infected host. L-SIGN (CD209L or DC-SIGNR) is a homolog of DC-SIGN, which is expressed in liver, lymph node, and placenta. L-SIGN acts in conjunction with the liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin) to enhance SARS-CoV infection. There is evidence to show that L-SIGN serves as an alternative receptor to mediate the entry of SARS-CoV.

Once infection can be established, the mechanisms by which SARS-CoV causes disease can be separated into (1) direct lytic effects on host cells and (2) indirect consequences resulting from the host immune response. Clinically, SARS is characterized by a pronounced systemic illness, but the pathology of SARS, as revealed from fatal cases, was mainly confined to the lungs, where diffuse alveolar damage was the most prominent feature. Multinucleated syncytial giant cells, although characteristic,
were rarely seen. In cases without secondary infection, a lack of immune response was observed at this late terminal stage. Apart from those related to end-stage multiorgan failure, the pathologies of gastrointestinal tract, urinary system, liver, and other organ systems were unremarkable. Lungs and intestinal tract are the only 2 organ systems that support high levels of SARS-CoV replication.

At least 2 mechanisms of direct injury in infected lungs have been revealed. First, in addition to being the host receptor mediating the entry of SARS-CoV, the ACE2 probably contributes to the diffuse alveolar damage. ACE2 is a negative regulator of the local renin-angiotensin system, where its imbalance leads to the development of diffuse alveolar damage. Data from animal studies suggest that the diffuse alveolar damage seen in SARS is mediated by the S protein-ACE2-renin-angiotensin pathway. The second direct injury mechanism is by the induction of apoptosis. The SARS-CoV-encoded 3a and 7a proteins have been shown to be a strong inducer of apoptosis in cell lines derived from different organs including lungs, kidneys, and liver.

IMMUNOBIOLOGY

Clinically, SARS is characterized by a phase of cytokine storm. The intense immune response to infection, as reflected by the increase in chemokines and cytokines, results in the pathology seen in cases that run a severe course of illness. In post-mortem lung tissues, chemokine C-X-C motif ligand (CXCL)-10 (or interferon [IFN]-inducible protein [IP] 10) and interleukin (IL)-18 were found to be increased. During the first 2 weeks, a variety of cytokines/chemokines were found to be increased in the peripheral circulation, including CXCL-9 (chemokine C-X-C motif ligand 2 or monokine induced by γ-IFN), CXCL-10 (or IP-10), and C-C motif ligand (CCL)-2 or monocyte chemoattractant protein-1 (MCP-1), IL-1β, IL-6, IL-8 (CXCL-8), IL-12, IFN-γ, transforming growth factor (TGF)-β, monokine induced by IFN-γ (MIG, CXCL-9). Among these increased cytokines/chemokines, increased levels of IP-10, MIG, and IL-8 during the first week after the onset of fever and increase of MIG during the second week were associated with poor outcome.

Several host genetic markers have been reported to have an association with the outcome of SARS. An association of HLA-B*4601 with SARS infection was revealed from a cohort of patients from Taiwan, but the finding was not reproduced in HK patients. In the latter HK study, HLA-B*0703 was found to be associated with an increased susceptibility, whereas HLA-DRB1*0301 was protective against SARS-CoV infection. In another study based on patients from HK, it was shown that the human Fc γ-receptor genotype, FcγRIA-R/R131 and CD14-159CC were associated with more severe outcome of SARS. RANTES-28 CG and GG genotypes were found to be associated with an increased susceptibility to SARS. In a cohort study of SARS patients in HK, an association between CLEC4M homozygosity and protection against SARS was found. However, the observation could not be reproduced in 2 other studies in HK and Beijing, respectively.

TREATMENT

Ribavirin

Ribavirin, a nucleoside analogue that has activity against several viruses in vitro, was widely used for treating SARS patients after recognizing the lack of clinical response to broad-spectrum antibiotics and oseltamivir. Nevertheless, it is now known that ribavirin has no significant in vitro activity against SARS-CoV. Hemoglobin levels in about 60% of patients dropped by 2 g/dL after 2 weeks of oral ribavirin therapy, at a dose of 1.2 g 3 times a day. The use of ribavirin for SARS in Toronto
was based on the higher dosage used for treating hemorrhagic fever, which led to more toxicity, including increased liver transaminases and bradycardia. Furthermore, addition of ribavirin did not have any useful effect on the serum SARS-CoV viral load of pediatric SARS patients. Therefore, it is unlikely that ribavirin alone has any significant clinical benefits in the treatment of SARS.

**Protease Inhibitors**

Genomic analysis of the SARS-CoV has revealed several enzymatic targets including protease. Lopinavir and ritonavir in combination is a boosted protease inhibitor regimen widely used in the treatment of human immunodeficiency virus (HIV) infection. In vitro activity against SARS-CoV was shown for lopinavir and ribavirin at 4 μg/mL and 50 μg/mL, respectively. Inhibition of in vitro cytopathic effects was achieved down to a concentration of 1 μg/mL of lopinavir combined with 6.25 μg/mL of ribavirin. Therefore, the data suggest that this combination might be synergistic against SARS-CoV in vivo. The addition of lopinavir 400 mg/ritonavir 100 mg (LPV/r) as initial therapy was associated with significant reduction in overall death rate (2.3% vs 15.6%) and intubation rate (0% vs 11%) compared with a matched historical cohort that received ribavirin alone as the initial antiviral therapy. Other reported beneficial effects include a reduction in corticosteroid use, fewer nosocomial infections, a decreasing viral load, and rising peripheral lymphocyte count.

In contrast, the outcome of the subgroup who had received LPV/r as rescue therapy after receiving pulsed methylprednisolone (MP) treatment of worsening respiratory symptoms was not better than the matched cohort. The improved clinical outcome in patients who received LPV/r as part of the initial therapy may be the result of peak (9.6 μg/mL) and trough (5.5 μg/mL) serum concentrations of lopinavir inhibiting the virus. Nelfinavir, another protease inhibitor commonly used for HIV infection, was shown to inhibit replication of SARS-CoV in Vero cell culture.

**IFNs**

Type 1 IFNs, such as IFN-α, are produced early as part of the innate immune response to virus infections. Type 1 IFNs inhibit a wide range of RNA and DNA viruses including SARS-CoV in vitro. Complete inhibition of cytopathic effects of SARS-CoV in culture was observed for IFN subtypes, α-1b, α-n1, α-n3, and human leukocyte IFN-α. IFN-α showed an in vitro inhibitory effect on SARS-CoV starting at concentrations of 1000 IU/mL, whereas recombinant human IFN-β 1a potently inhibited SARS-CoV in vitro. IFN-β and IFN-γ can synergistically inhibit the replication of SARS-CoV in vitro. In addition, a combination of ribavirin and IFN-β has been shown to have synergistic effects in inhibiting SARS-CoV in animal and human cell lines, whereas combinations of ribavirin with IFN-β 1a or IFN-α also show synergistic effects in vitro.

In experimentally infected cynomolgus macaques, prophylactic treatment with pegylated IFN-α significantly reduced viral replication and excretion, viral antigen expression by type 1 pneumocytes, and pulmonary damage, compared with untreated macaques, whereas postexposure treatment with pegylated IFN-α yielded intermediate results. Use of IFN-α 1 plus corticosteroids was associated with improved oxygen saturation, more rapid resolution of radiographic lung opacities, and lower levels of CPK in SARS patients. These findings support clinical testing of approved IFNs for the treatment of SARS.

**Human Monoclonal Antibody**

There is evidence that SARS-CoV infection is initiated through binding of the SARS-CoV S protein to ACE2. A high-affinity human monoclonal antibody (huMab) termed
80R has been identified against the SARS-CoV S protein and has potent neutralizing activity in vitro and in vivo.\textsuperscript{120} HuMab 80R efficiently neutralized SARS-CoV and inhibited syncytia formation between cells expressing the S protein and those expressing the SARS-CoV receptor ACE2. HuMab 80R may be a useful viral entry inhibitor for the emergency prophylaxis and treatment of SARS.\textsuperscript{120} HuMab was shown to prophylactically reduce replication of SARS-CoV in the lungs of infected ferrets and abolish shedding of viruses in pharyngeal secretions, in addition to completely preventing SARS-CoV–induced macroscopic lung pathology.\textsuperscript{121}

**Vaccines**

An adenovirus-based vaccine was shown to induce strong SARS-CoV–specific immune responses in rhesus macaques, and holds promise for the development of a protective vaccine against SARS-CoV.\textsuperscript{122} A DNA vaccine based on the S gene could induce the production of specific IgG antibody against SARS-CoV efficiently in mice, with a seroconversion rate of 75% after 3 doses of immunization.\textsuperscript{123,124} Recombinant S proteins that exhibit antigenicity and receptor-binding ability are also good candidates for developing a SARS vaccine.\textsuperscript{125} A recombinant attenuated vaccinia virus, Ankara, expressing the S protein of SARS-CoV can elicit protective immunity in mice.\textsuperscript{126} Another recombinant attenuated parainfluenza virus expressing the S protein also produced immunity following intranasal inoculation to mice.\textsuperscript{127} Synthetic peptide derived from the S protein is another target for vaccine development. Promising results have been obtained in vitro\textsuperscript{128} and in vivo from rabbit and monkey models.\textsuperscript{129}

**Systemic Corticosteroids**

During phase II of the clinical course, when patients progress to develop pneumonia and hypoxemia, intravenous administration of rescue pulsed MP has been shown to suppress cytokine-induced lung injury.\textsuperscript{1,35,106,109,130} The rationale could be that the progression of the pulmonary disease is mediated by the host inflammatory response.\textsuperscript{35} Corticosteroids significantly reduced IL-8, MCP-1, and IFN–γ IP-10 concentrations from 5 to 8 days after treatment in 20 adult SARS patients.\textsuperscript{89} Induction of IP-10 is believed to be a critical event in the initiation of immune-mediated lung injury and lymphocyte apoptosis.\textsuperscript{90}

The use of rescue pulsed MP during clinical progression was associated with favorable clinical improvement with resolution of fever and lung opacities within 2 weeks.\textsuperscript{1,106,130} However, a retrospective analysis showed that the use of pulsed MP was associated with an increased risk of 30-day mortality (adjusted OR 26.0, 95% CI 4.4–154.8).\textsuperscript{131} This retrospective study could not establish whether a causal relationship existed between the use of MP and an increased risk of death, as clinicians were more inclined to give pulsed MP therapy in deteriorating patients. Nevertheless, complications such as disseminated fungal disease\textsuperscript{132} and avascular necrosis of bone have been reported following prolonged corticosteroid therapy.\textsuperscript{133} With the rescue pulsed MP approach, avascular necrosis of bone was found in 12 (4.7%) patients after screening 254 using magnetic resonance imaging. The risk of avascular necrosis was 0.6% for patients receiving less than 3 g, and was 13% for those receiving more than 3 g prednisolone–equivalent dose.\textsuperscript{134} A randomized placebo-controlled study conducted at PWH, HK 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 in those given normal saline (n = 7) during phase I of the clinical course of illness.\textsuperscript{135} Despite the small sample size, the data suggest that pulsed MP given in the earlier phase might prolong viremia and thus it should only be given during the later phase for rescue purposes. Carefully designed clinical trials with larger sample sizes
are required to determine the optimal timing and dosage of systemic steroid in the treatment of possibly immune-mediated lung injury in SARS.

**Convalescent Plasma**

Convalescent plasma, donated by patients who have recovered from SARS, contains neutralizing antibody and may be clinically useful for treating other SARS patients.\textsuperscript{136,137}

**Traditional Chinese Medicine**

Glycyrrhizin, an active component of liquorice roots, was shown to inhibit the replication of SARS-CoV in vitro.\textsuperscript{103} A controlled study comparing integrative Chinese and Western medicine with Western medicine alone suggested that the combination treatment given in phase I of SARS was more effective in reducing the number of patients with abnormal oxygen saturations.\textsuperscript{138} However, it was not clear which of the Chinese medicine components was responsible for the benefit, and the dosage of steroid given to the groups was not clear.

**Intravenous Gammaglobulin and Pentaglobulin**

Intravenous gammaglobulin (IVIg) has immunomodulatory properties and may down-regulate cytokine expression.\textsuperscript{139} It was used extensively in Singapore during the SARS outbreak in 2003. However, it was noted that one-third of critically ill patients developed venous thromboembolism, including pulmonary embolism, despite prophylactic use of low-molecular-weight heparin.\textsuperscript{140} There was evidence of pulmonary embolism in 4 out of 8 postmortem cases.\textsuperscript{141} In addition, there were 5 cases of large artery ischemic stroke, of which 3 cases had been given IVIg.\textsuperscript{142} Pentaglobulin (IgM enriched Ig) was administered to 12 patients with SARS who continued to deteriorate despite pulsed steroid and ribavirin, and its use was associated with subsequent improvement in oxygenation and radiographic scores. It was difficult to judge its effects because the study was uncontrolled and pulsed steroid was used concurrently.\textsuperscript{143} Pulmonary artery thrombosis was reported in a patient with SARS who had been treated with ribavirin, steroid, kaletra, IVIg, and pentaglobulin.\textsuperscript{144} It is possible that IVIg- or pentaglobulin-induced increase in viscosity may be consequential in patients with hypercoagulable states such as SARS.\textsuperscript{145}

**Nitric Oxide**

Inhaled nitric oxide (NO) was reported to have beneficial effects in SARS. In a controlled study comparing the use of NO (n = 6) and supportive treatment (n = 8) for severe respiratory failure, there was improvement in oxygenation after inhaled NO was administered, and this allowed ventilatory support to be discontinued. The beneficial effects persisted after termination of NO inhalation.\textsuperscript{146} NO has been shown to inhibit the replication cycle of SARS-CoV in vitro.\textsuperscript{147}

**OUTCOMES**

**Short-term**

Based on the data received by the World Health Organization, the case fatality rate for SARS was less than 1% for patients aged 24 years or younger, 6% for 25 to 44 years, 15% for 45 to 64 years, and more than 50% for patients aged 65 years or older.\textsuperscript{148} Poor prognostic factors for more severe disease included advanced age,\textsuperscript{1,35,149,150} chronic hepatitis B treated with lamivudine,\textsuperscript{35} severe hepatitis,\textsuperscript{37} high initial LDH,\textsuperscript{150} high peak LDH,\textsuperscript{1} high neutrophil count on presentation,\textsuperscript{1,150} diabetes mellitus or other
comorbid conditions, low CD4 and CD8 lymphocyte counts at presentation, and a high initial SARS-CoV viral load.

**Long-term**

Significant impairment of the diffusing capacity of carbon monoxide in the lung (DLCO) occurred in 15.5% and 23.7% of SARS survivors at the PWH cohort at 6 and 12 months, respectively. Although significant improvement in serial chest radiography was observed among the SARS survivors, 27.8% still had abnormal radiographic scores at 12 months. Despite the presence of extensive parenchymal changes revealed by computer tomography during the early convalescent period, most SARS survivors had lung function test indices within normal limits. However, their exercise ability (6-minute walk distance) at 12 months after illness onset was lower than the general population. The functional disability seems out of proportion to the degree of lung function impairment and might be caused by extrapulmonary factors such as muscle deconditioning and steroid myopathy. Critical illness associated polyneuropathy/mypoathy was also observed in a few SARS survivors. The reported incidence rates of avascular necrosis of bone among different cohorts in HK ranged from 4.7% to 15%, whereas 1 study from Beijing reported a high incidence of 42%.

Several other groups have shown that persistent lung function abnormalities occur in less than one-third of patients at 1 year and that there was significant impairment of health status among SARS survivors and their carers. The physical impairment and the long period of isolation and extreme uncertainty during the SARS illness created enormous psychological stress and mood disturbances. In addition, steroid toxicity, personal vulnerability, and psychosocial stressors might have jointly contributed to the development of psychosis in some patients.

**VACCINE DEVELOPMENT**

Various forms of SARS-CoV vaccine have been evaluated. Inactivated whole virus vaccines are immunogenic and protective in animal models. However, this approach requires the production of a large amount of infectious virus in a biosafety level 3 containment facility, which is not widely available among vaccine manufacturers. Because the S protein of SARS-CoV is responsible for receptor binding and membrane fusion, it is a priority target for the development of subunit vaccines. Full-length S protein delivered in the form of DNA vaccine, or expressed in attenuated vaccinia virus or recombinant baculovirus systems, have been shown to induce T cell and neutralizing antibody responses, and have been found to be protective in challenge studies. However, there are concerns about using full-length S protein as a vaccine, because harmful immune responses causing liver damage in vaccinated animals have been reported. The possibility of enhanced disease, as observed in vaccinated cats on infection with feline infectious peritonitis virus, is also a concern. Theoretically, antibodies present at low concentrations may form complexes with virions, and be taken up by macrophage via the Fc receptors expressed on its surface. This process enhances virus dissemination and may lead to adverse outcomes. Vaccines based on a partial S protein or other structural proteins of SARS-CoV have been explored. The greatest challenge to sustainable vaccine development is that SARS-CoV has disappeared from humans, and antigenic changes of the re-emergent strain, if it ever occurs, remain unknown.
SUMMARY

SARS is a highly infectious disease with a significant morbidity and mortality. Respiratory failure is the major complication, and 20% of patients may progress to ARDS. HCWs are particularly vulnerable to SARS as the viral loads of SARS-CoV in patients increase to peak levels during the second week after patients are hospitalized.35,169 Because SARS has the potential to be converted from droplet to airborne transmission, HCWs should use adequate respiratory protection, in addition to strict contact and droplet precautions, when managing patients with SARS. Because there is currently no proven effective treatment of SARS, early recognition, isolation, and stringent infection control measures are the key to controlling this highly contagious disease. Isolation facilities, strict droplet and contact precautions (hand hygiene, gown, gloves, N95 masks, eye protection) for HCWs managing patients with SARS, avoidance of using jet nebulizers on general wards,1,27,52 contact tracing, and quarantine isolation for close contacts are important measures in controlling the spread of the infection in hospitals and the community.

The presence of SARS-like CoVs in horseshoe bats implicates bats in previous and potentially future emergence of novel CoV infection in humans. Public health measures should be enforced to ban the trading of wild animals in wet markets in South China, where SARS-CoV infection started. When evaluating epidemiologically high-risk patients with community-acquired pneumonia and no immediate alternative diagnosis, a low ANC on presentation, along with poor responses after 72 hours of antibiotic treatment, may raise the index of suspicion for SARS. Further studies are needed to examine host genetic markers that may predict clinical outcome.

REFERENCES

1. Lee N, Hui DS, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1986–94.
2. Hsu LY, Lee CC, Green JA, et al. Severe acute respiratory syndrome in Singapore: clinical features of index patient and initial contacts. Emerg Infect Dis 2003;9:713–7.
3. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 2003; 289:2801–9.
4. Twu SJ, Chen TJ, Chen CJ, et al. Control measures for severe acute respiratory syndrome (SARS) in Taiwan. Emerg Infect Dis 2003;9:718–20.
5. WHO. Summary of probable SARS cases with onset of illness from 1 November to 31 July 2003. Available at: http://www.who.int/csr/sars/country/table2003_09_23/en. Accessed September 23, 2003.
6. Wang M, Yan M, Xu H, et al. SARS-CoV infection in a restaurant from palm civet. Emerg Infect Dis 2005;11:1860–5.
7. Che XY, Di B, Zhao GP, et al. A patient with asymptomatic severe acute respiratory syndrome (SARS) and antigenemia from the 2003–2004 community outbreak of SARS in Guangzhou, China. Clin Infect Dis 2006;43:e1–5.
8. Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319–25.
9. Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003;362:263–70.
10. Drosten C, Gunther S, Preiser W, et al. Identification of a novel Coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003;348:1967–76.
11. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel Coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953–66.
12. Fouchier RA, Kuiken T, Schutten M, et al. Aetiology: Koch’s postulates fulfilled for SARS virus. Nature 2003;423:240.
13. Rota PA, Oberste MS, Monroe SS, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science 2003;300:1394–9.
14. Marra MA, Jones SJ, Astell CR, et al. The genome sequence of the SARS-associated coronavirus. Science 2003;300:1399–404.
15. Ruan YJ, Wei CL, Ee LA, et al. Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection. Lancet 2003;361:1779–85.
16. Du L, Qiu JC, Wang M, et al. Analysis on the characteristics of blood serum Ab-IgG detective result of severe acute respiratory syndrome patients in Guangzhou, China. Zhonghua Liu Xing Bing Xue Za Zhi 2004;25:925–8.
17. Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in Southern China. Science 2003;302:276–8.
18. Song HD, Tu CC, Zhang, et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci U S A 2005;102:2430–5.
19. Lau SK, Woo PC, Li KS, et al. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci U S A 2005;102:14040–5.
20. Li W, Shi Z, Yu M, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science 2005;310:676–9.
21. Shi Z, Hu Z. A review of studies on animal reservoirs of the SARS coronavirus. Virus Res 2008;133:74–87.
22. Zhao Z, Zhang F, Xu M, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. J Med Microbiol 2003;52:715–20.
23. Xu RH, He JF, Evans MR, et al. Epidemiologic clues to SARS origin in China. Emerg Infect Dis 2004;10:1030–7.
24. Zhong NS, Zheng BJ, Li YM, et al. Epidemiology and cause of severe acute respiratory syndrome in Guangdong, People’s Republic of China, in 2003. Lancet 2003;362:1353–8.
25. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1977–85.
26. Peiris JS, Yuen KY, Osterhaus AD, et al. The severe acute respiratory syndrome. N Engl J Med 2003;349:2431–41.
27. Wong RS, Hui DS. Index patient and SARS outbreak in Hong Kong. Emerg Infect Dis 2004;10:339–41.
28. Loon SC, Teoh SC, Oon LL, et al. The severe acute respiratory syndrome coronavirus in tears. Br J Ophthalmol 2004;88:861–3.
29. Yu IT, Li Y, Wong TW, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med 2004;350:1731–9.
30. Chu CM, Cheng VC, Hung IF, et al. Viral load distribution in SARS outbreak. Emerg Infect Dis 2005;11:1882–6.
31. Booth TF, Kournikakis B, Bastien N, et al. Detection of airborne severe acute respiratory syndrome (SARS) coronavirus and environmental contamination in SARS outbreak units. J Infect Dis 2005;191:1472–7.
32. Yu IT, Wong TW, Chiu YL, et al. Temporal-spatial analysis of severe acute respiratory syndrome among hospital inpatients. Clin Infect Dis 2005;40:1237–43.
33. Leung GM, Hedley AJ, Ho LM, et al. The epidemiology of severe acute respiratory syndrome in the 2003 Hong Kong epidemic: an analysis of all 1755 patients. Ann Intern Med 2004;141:662–73.
34. Hui DS, Wong PC, Wang C. Severe acute respiratory syndrome: clinical features and diagnosis. Respirology 2003;8:S20–4.
35. Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767–72.
36. Leung WK, To KF, Chan PK, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterologist 2003;125:1011–7.
37. Chan HL, Kwan AC, To KF, et al. Clinical significance of hepatic derangement in severe acute respiratory syndrome. World J Gastroenterol 2005;11:2148–53.
38. Hung EC, Chim SS, Chan PK, et al. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. Clin Chem 2003;49:2108–9.
39. Lau KK, Yu WC, Chu CM, et al. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis 2004;10:342–4.
40. Wong KC, Leung KS, Hui M. Severe acute respiratory syndrome (SARS) in a geriatric patient with a hip fracture. A case report. J Bone Joint Surg Am 2003;85:1339–42.
41. Lee AK, Oh HM, Hui KP, et al. Atypical SARS in a geriatric patient. Emerg Infect Dis 2004;10:261–4.
42. Fisher DA, Lim TK, Lim YT, et al. Atypical presentations of SARS. Lancet 2003;361:1740.
43. Hon KL, Leung CW, Cheng WT, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet 2003;561:1701–3.
44. Sit SC, Yau EKC, Lam YY, et al. A young infant with severe acute respiratory syndrome. Pediatrics 2003;112:e257–60.
45. Bitnun A, Allen U, Heurter H, et al. Children hospitalized with severe acute respiratory syndrome-related illness in Toronto. Pediatrics 2003;112:e261–8.
46. Chiu WK, Cheung PC, Ng KL, et al. Severe acute respiratory syndrome in children: experience in a regional hospital in Hong Kong. Pediatr Crit Care Med 2003;4:279–83.
47. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 2004;191:292–7.
48. Xu JL, Qi X, Chi J, et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod 2006;74:410–6.
49. Leung GM, Lim WW, Ho LM, et al. Seroprevalence of IgG antibodies to SARS-coronavirus in asymptomatic or subclinical population groups. Epidemiol Infect 2006;134:211–21.
50. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? Clin Infect Dis 2007;44:1017–25.
51. Hui DS, Hall SD, Chan MT, et al. Exhaled air dispersion during oxygen delivery via a simple oxygen mask. Chest 2007;132:540–6.
52. Hui DS, Chow BK, Hall SD, et al. Exhaled air and aerosolized droplet dispersion during application of a jet nebulizer. Chest 2009;135:648–54.
53. Hui DS, Hall SD, Chan MT, et al. Non-invasive positive pressure ventilation: an experimental model to assess air and particle dispersion. Chest 2006;130:730–40.

54. Hui DS, Chow BK, Hall SD, et al. Exhaled air dispersion distances during application of non-invasive ventilation via different Respironics face masks. Chest 2009;167:348–53.

55. Hui DS, Wong KT, Antonio GE, et al. Severe acute respiratory syndrome (SARS): correlation of clinical outcome and radiological features. Radiology 2004;233:579–85.

56. Hui DS, Sung JJ. Severe acute respiratory syndrome. Chest 2003;124:12–5.

57. Wong GW, Hui DS. Severe acute respiratory syndrome: epidemiology, diagnosis and treatment. Thorax 2003;58:558–60.

58. Wong RS, Wu A, To KF, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. Br Med J 2003;326:1358–62.

59. Chen X, Zhou B, Li M, et al. Serology of severe acute respiratory syndrome: implications for surveillance and outcome. J Infect Dis 2004;189:1158–63.

60. Muller MP, Tomlinson G, Marrie TJ, et al. Can routine laboratory tests discriminate between severe acute respiratory syndrome and other causes of community acquired pneumonia? Clin Infect Dis 2005;40:1079–86.

61. Lee N, Rainer TH, Ip M, et al. Role of laboratory variables in differentiating SARS-coronavirus from other causes of community-acquired pneumonia within the first 72 hrs of hospitalization. Eur J Clin Microbiol Infect Dis 2006;25:765–72.

62. Rainer TH, Lee N, Ip M, et al. Features discriminating SARS from other severe viral respiratory tract infections. Eur J Clin Microbiol Infect Dis 2007;26:121–9.

63. Wong KT, Antonio GE, Hui DS, et al. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 Patients. Radiology 2003;228:401–6.

64. Gomersall CD, Joynt GM, Lam P, et al. Short-term outcome of critically ill patients with severe acute respiratory syndrome. Intensive Care Med 2004;30:381–7.

65. Wong KT, Antonio GE, Hui DS, et al. Thin section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. Radiology 2003;228:395–400.

66. Chan PK, To KF, Lo AW, et al. Persistent infection of SARS coronavirus in colonic cells in vitro. J Med Virol 2004;74:1–7.

67. Simmons G, Gosalia DN, Rennekamp AJ, et al. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc Natl Acad Sci U S A 2005;102:11876–81.

68. Tripet B, Howard MW, Jobling M, et al. Structural characterization of the SARS-coronavirus spike S fusion protein core. J Biol Chem 2004;279:20836–49.

69. Hofmann H, Pöhlmann S. Cellular entry of the SARS coronavirus. Trends Microbiol 2004;12:466–72.

70. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450–4.

71. Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631–7.

72. Tang JW, To KF, Lo AW, et al. Quantitative temporal-spatial distribution of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) in post-mortem tissues. J Med Virol 2007;79:1245–53.
73. Yang ZY, Huang Y, Ganesh L, et al. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN. J Virol 2004;78:5642–50.
74. Gramberg T, Hofmann H, Möller P, et al. LSECtin interacts with filovirus glycoproteins and the spike protein of SARS coronavirus. Virology 2005;340:224–36.
75. van Kooyk Y, Geijtenbeek TB. DC-SIGN: escape mechanism for pathogens. Nat Rev Immunol 2003;3:697–709.
76. Jeffers SA, Tusell SM, Gillim-Ross L, et al. CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus. Proc Natl Acad Sci U S A 2004;101:15748–53.
77. Marzi A, Gramberg T, Simmons G, et al. DC-SIGN and DC-SIGNR interact with the glycoprotein of Marburg virus and the S protein of severe acute respiratory syndrome coronavirus. J Virol 2004;78:12090–5.
78. Lo AW, Tang NL, To KF. How the SARS coronavirus causes disease: host or organism? J Pathol 2006;208:142–51.
79. Ng WF, To KF, Lam WW, et al. The comparative pathology of severe acute respiratory syndrome and avian influenza A subtype H5N1—a review. Hum Pathol 2006;37:381–90.
80. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Am J Pathol 2007;170:1136–47.
81. Cameron MJ, Bermejo-Martin JF, Danesh A, et al. Human immunopathogenesis of severe acute respiratory syndrome (SARS). Virus Res 2007;133:13–9.
82. Guo Y, Korteweg C, McNutt MA, et al. Pathogenetic mechanisms of severe acute respiratory syndrome. Virus Res 2007;133:4–12.
83. To KF, Tong JH, Chan PK, et al. Tissue and cellular tropisms of the coronavirus associated with severe acute respiratory syndrome—an in-situ hybridization study of fatal cases. J Pathol 2004;202:157–63.
84. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436:112–6.
85. Burrell LM, Johnston CI, Tikellis C, et al. ACE2, a new regulator of the renin-angiotensin system. Trends Endocrinol Metab 2004;15:166–9.
86. Wong SL, Chen Y, Chan CM, et al. In vivo functional characterization of the SARS-Coronavirus 3a protein in Drosophila. Biochem Biophys Res Commun 2005;337:720–9.
87. Law PT, Wong CH, Au TC, et al. The 3a protein of severe acute respiratory syndrome-associated coronavirus induces apoptosis in Vero E6 cells. J Gen Virol 2005;86:1921–30.
88. Tan YJ, Fielding BC, Goh PY, et al. Over expression of 7a, a protein specifically encoded by the severe acute respiratory syndrome coronavirus, induces apoptosis via a caspase-dependent pathway. J Virol 2004;78:14043–7.
89. Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 2004;136:95–103.
90. Jiang Y, Xu J, Zhou C, et al. Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome. Am J Respir Crit Care Med 2005;171:850–7.
91. Huang KJ, Su IJ, Theron M, et al. An interferon-gamma-related cytokine storm in SARS patients. J Med Virol 2005;75:185–94.
92. Tang NL, Chan PK, Wong CK, et al. Early enhanced expression of IP-10 (CXCL-10) and other chemokines predict adverse outcome in severe acute respiratory syndrome (SARS). Clin Chem 2005;51:2333–40.
93. Zhang Y, Li J, Zhan Y, et al. Analysis of serum cytokines in patients with severe acute respiratory syndrome. Infect Immun 2004;72:4410–5.
94. Lau YL, Peiris JS. Pathogenesis of severe acute respiratory syndrome. Curr Opin Immunol 2005;17:404–10.
95. Lin M, Tseng HK, Trejaut JA, et al. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. BMC Med Genet 2003;4:9.
96. Ng MH, Lau KM, Li L, et al. Association of human-leukocyte-antigen class I (B\*0703) and class II (DRB1\*0301) genotypes with susceptibility and resistance to the development of severe acute respiratory syndrome. J Infect Dis 2004;190:515–8.
97. Yuan FF, Tanner J, Chan PK, et al. Influence of FcγRIIA and MBL polymorphisms on severe acute respiratory syndrome. Tissue Antigens 2005;66:291–6.
98. Yuan FF, Boehm I, Chan PK, et al. High prevalence of the CD14-159CC genotype in patients infected with severe acute respiratory syndrome-associated coronavirus. Clin Vaccine Immunol 2007;14:1644–5.
99. Ng MW, Zhou G, Chong WP, et al. The association of RANTES polymorphism with severe acute respiratory syndrome in Hong Kong and Beijing Chinese. BMC Infect Dis 2007;7:50.
100. Chan VS, Chan KY, Chen Y, et al. Homozygous L-SIGN (CLEC4M) plays a protective role in SARS coronavirus infection. Nat Genet 2006;38:38–46.
101. Tang NL, Chan PK, Hui DS, et al. Lack of support for an association between CLEC4M homozygosity and protection against SARS coronavirus infection. Nat Genet 2007;39:691–2.
102. Zhi L, Zhou G, Zhang H, et al. Lack of support for an association between CLEC4M homozygosity and protection against SARS coronavirus infection. Nat Genet 2007;39:692–4.
103. Cinatl J, Morgenstern B, Bauer G, et al. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 2003;361:2045–6.
104. Tan EL, Ooi EE, Lin CY, et al. Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. Emerg Infect Dis 2004;10:581–6.
105. Stroher U, DiCaro A, Li Y, et al. Severe acute respiratory syndrome-related coronavirus is inhibited by interferon-α. J Infect Dis 2004;189:1164–7.
106. Sung JJ, Wu A, Joynt GM, et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. Thorax 2004;59:414–20.
107. Ng EK, Ng PC, Hon KL, et al. Serial analysis of the plasma concentration of SARS coronavirus RNA in pediatric patients with severe acute respiratory syndrome. Clin Chem 2003;49:2085–8.
108. Anand K, Ziebuhr J, Wadhwani P, et al. Coronavirus main proteinase (3Clpro) structure: basis for design of anti-SARS drugs. Science 2003;300:1763–7.
109. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252–6.
110. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicenter retrospective matched cohort study. Hong Kong Med J 2003;9:399–406.
111. Hurst M, Faulds D. Lopinavir. Drugs 2000;60:1371–81.
112. Yamamoto N, Yang R, Yoshinaka Y, et al. HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. Biochem Biophys Res Commun 2004;318:719–25.
113. Cinatl J, Morgenstern B, Bauer G, et al. Treatment of SARS with human interferons. Lancet 2003;362:293–4.
114. Hensley LE, Fritz LE, Jahrling PB, et al. Interferon-β 1a and SARS coronavirus replication. Emerg Infect Dis 2004;10:317–9.
115. Sainz B Jr, Mossel EC, Peters CJ, et al. Interferon-beta and interferon-gamma synergistically inhibit the replication of severe acute respiratory syndrome-associated coronavirus (SARS-CoV). Virology 2004;329:11–7.

116. Morgenstern B, Michaelis M, Baer PC, et al. Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. Biochem Biophys Res Commun 2005;326:905–8.

117. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2005;39:69–75.

118. Haagmans BL, Kuiken T, Martina BE, et al. Pegylated interferon-α protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat Med 2004;10:290–3.

119. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA 2003;290:3222–8.

120. Sui J, Li W, Murakami A, et al. Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. Proc Natl Acad Sci U S A 2004;101:2536–41.

121. ter Meulen J, Bakker AB, van den Brink EN, et al. Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. Lancet 2004;363:2139–41.

122. Gao W, Tamin A, Soloff A, et al. Effects of a SARS-associated coronavirus vaccine in monkeys. Lancet 2003;362:1895–6.

123. Zhao P, Ke JS, Qin ZL, et al. DNA vaccine of SARS-CoV S gene induces antibody response in mice. Acta Biochim Biophys Sin (Shanghai) 2004;36:37–41.

124. Yang ZY, Kong WP, Huang Y, et al. A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. Nature 2004;428:561–4.

125. Ho TY, Wu SL, Cheng SE, et al. Antigenicity and receptor-binding ability of recombinant SARS coronavirus spike protein. Biochem Biophys Res Commun 2004;313:938–47.

126. Bisht H, Roberts A, Vogel L, et al. Severe acute respiratory syndrome coronavirus spike protein expressed by attenuated vaccinia virus protectively immunizes mice. Proc Natl Acad Sci U S A 2004;101:6641–6.

127. Bukreyev A, Lamirande EW, Buchholz UJ, et al. Mucosal immunisation of African green monkeys (Cercopithecus aethiops) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. Lancet 2004;363:2122–7.

128. Bosch BJ, Martina BE, van der Zee R, et al. Severe acute respiratory syndrome coronavirus (SARS-CoV) infection inhibition using spike protein heptad repeat-derived peptides. Proc Natl Acad Sci U S A 2004;101:8455–60.

129. Choy WY, Lin SG, Chan PK, et al. Synthetic peptide studies on the severe acute respiratory syndrome (SARS) coronavirus spike glycoprotein: perspective for SARS vaccine development. Clin Chem 2004;50:1036–42.

130. Ho JC, Ooi GC, Mok TY, et al. High dose pulse versus non-pulse corticosteroid regimens in severe acute respiratory syndrome. Am J Respir Crit Care Med 2003;168:1449–56.

131. Tsang OT, Chau TN, Choi KW, et al. Coronavirus-positive nasopharyngeal aspirate as predictor for severe acute respiratory syndrome mortality. Emerg Infect Dis 2003;9:1381–7.

132. Wang H, Ding Y, Li X, et al. Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. N Engl J Med 2003;349:507–8.
133. Hong N, Du XK. Avascular necrosis of bone in severe acute respiratory syndrome. Clin Radiol 2004;59:602–8.
134. Griffith JF, Antonio GE, Kumta SM, et al. Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. Radiology 2005;235:168–75.
135. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol 2004;31:304–9.
136. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44–6.
137. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 2004;10:676–8.
138. Liu BY, Hu JQ, Xie YM, et al. Effects of integrative Chinese and Western medicine on arterial oxygen saturation in patients with severe acute respiratory syndrome. Chin J Integr Med 2004;10:117–22.
139. Ballow M. Mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory diseases. J Allergy Clin Immunol 1997;100:151–7.
140. Lew TW, Kwek TK, Tai D, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. JAMA 2003;290:374–80.
141. Chong PY, Chui P, Ling AE, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. Arch Pathol Lab Med 2004;128:195–204.
142. Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol 2004;251:1227–31.
143. Ho JC, Wu AY, Lam B, et al. Pentaglobulin in steroid-resistant severe acute respiratory syndrome. Int J Tuberc Lung Dis 2004;8:1173–9.
144. Ng KH, Wu AK, Cheng VC, et al. Pulmonary artery thrombosis in a patient with severe acute respiratory syndrome. Postgrad Med J 2005;81:e3.
145. Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. Neurology 2003;60:1763–7.
146. Chen L, Liu P, Gao H, et al. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. Clin Infect Dis 2004;39:1531–5.
147. Akerstrom S, Mousavi-Jazi M, Klingstrom J, et al. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. J Virol 2005;79:1966–9.
148. WHO. SARS case fatality ratio, incubation period. Available at: http://www.who.int/csr/sars/archive/2003_05_07a/en/print.html. Accessed May 23, 2005.
149. Donnelly CA, Ghani AV, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 2003;361:1761–6.
150. Tsui PT, Kwok ML, Yuen H, et al. Severe acute respiratory syndrome: clinical outcome and prognostic correlates. Emerg Infect Dis 2003;9:1064–9.
151. Chan JW, Ng CK, Chan YH, et al. Short term outcome and risk factors for adverse clinical outcomes in adults with Severe acute respiratory syndrome (SARS). Thorax 2003;58:686–9.
152. Chu CM, Poon LL, Cheng VC, et al. Initial viral load and the outcomes of SARS. CMAJ 2004;171:1349–52.
153. Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax 2005;60:401–9.
154. Hui DS, Wong KT, Ko FW, et al. The one-year impact of severe acute respiratory syndrome (SARS) on pulmonary function, exercise capacity and quality of life in a cohort of survivors. Chest 2005;128:2247–61.
155. Tsai LK, Hsieh ST, Chao CC, et al. Neuromuscular disorders in survivors of severe acute respiratory syndrome. Arch Neurol 2004;61:1669–73.
156. Yu WC, Hui DS, Chan-Yeung M. Antiviral agents and corticosteroids in the treatment of SARS. Thorax 2004;59:643–5.
157. Tsang KW, Ooi GC, Ho PL. Diagnosis and pharmacotherapy of severe acute respiratory syndrome: what have we learnt? Eur Respir J 2004;24:1025–32.
158. Ong KC, Ng AW, Lee LS, et al. 1-year pulmonary function and health status in survivors of severe acute respiratory syndrome. Chest 2005;128:1393–400.
159. Xie L, Liu Y, Xiao Y, et al. Follow-up study on pulmonary function and lung radiographic changes in survivors of severe acute respiratory syndrome patients after discharge. Chest 2005;127:2119–24.
160. Tansey CM, Louie M, Loeb M, et al. One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. Arch Intern Med 2007;167:1312–20.
161. Chua SE, Cheung V, McAlonan GM, et al. Stress and psychological impact on SARS patients during the outbreak. Can J Psychiatry 2004;49:385–90.
162. Cheng SK, Wong CW, Tsang J, et al. Psychological distress and negative appraisals in survivors of severe acute respiratory syndrome (SARS). Psychol Med 2004;34:1187–95.
163. Lee DT, Wing YK, Leung HC, et al. Factors associated with psychosis among patients with severe acute respiratory syndrome: a case-control study. Clin Infect Dis 2004;39:1247–9.
164. Chen Z, Zhang L, Qin C, et al. Recombinant modified vaccinia virus Ankara expressing the spike glycoprotein of severe acute respiratory syndrome coronavirus induces protective neutralizing antibodies primarily targeting the receptor binding region. J Virol 2005;79:2678–88.
165. He Y, Li J, Heck S, et al. Antigenic and immunogenic characterization of recombinant baculovirus-expressed severe acute respiratory syndrome coronavirus spike protein: implication for vaccine design. J Virol 2006;80:5757–67.
166. Weingartl H, Czub M, Czub S, et al. Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. J Virol 2004;78:12672–6.
167. Petersen NC, Boyle JF. Immunologic phenomena in the effusive form of feline infectious peritonitis. Am J Vet Res 1980;41:868–76.
168. Vennema H, de Groot RJ, Harbour DA, et al. Early death after feline infectious peritonitis virus challenge due to recombinant vaccinia virus immunization. J Virol 1990;64:1407–9.
169. Chan PK, Ip M, Ng KC, et al. Severe acute respiratory syndrome-associated coronavirus infection. Emerg Infect Dis 2003;9:1453–4.