SARS: clinical presentation, transmission, pathogenesis and treatment options

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ABSTRACT

SARS (severe acute respiratory syndrome) appeared as the first emerging infectious disease of this century. It is fortunate that the culprit virus can be grown without much difficulty from a commonly used cell line, allowing an unlimited supply of isolates for further molecular studies and leading to the development of sensitive diagnostic assays. How the virus has successfully jumped the species barrier is still a mystery. The superspreading events that occurred within hospital, hotel and high-density housing estate opens a new chapter in the mechanisms and routes of virus transmission. The old practice of quarantine proved to be still useful in controlling the global outbreak. Despite all the available sophisticated tests, alertness with early recognition by healthcare workers and prompt isolation of suspected cases is still the most important step for containing the spread of the infection. Although the rapidly evolving outbreak did not allow the conducting of systematic clinical trails to evaluate treatment options, the accumulated experience on managing SARS patients will improve the clinical outcome should SARS return. Although SARS led to more than 700 deaths worldwide, the lessons learnt have prepared healthcare systems worldwide to face future emerging and re-emerging infections.

INTRODUCTION

An outbreak of atypical pneumonia of unknown aetiology occurred in November 2002 in Foshan, Guangdong Province in southern China [1,2]. The disease spread to Guangzhou in early 2003. In March 2003, similar outbreaks were noted in Vietnam, Hong Kong and Canada and subsequently involved more than 30 countries [3–6]. In view of the multiregion involvement and the severity of the disease, the WHO (World Health Organization) declared in early March 2003 that a global outbreak was occurring and set up a network of laboratories to investigate the cause as well as means to control the spread of the disease. The disease was officially named ‘severe acute respiratory syndrome’ (SARS). In late March 2003, a few laboratories independently identified

Key words: coronavirus, inflammation, respiratory infection, severe acute respiratory syndrome (SARS), viral transmission.

Abbreviations: ACE-II, angiotensin-converting enzyme 2; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; FIPV, feline infectious peritonitis virus; huMab, human monoclonal antibody; IFN, interferon; IL, interleukin; IP-10, IFN-γ-inducible protein-10; IVIg, intravenous γ-globulin; LDH, lactate dehydrogenase; LPV/r, 400 mg of lopinavir/100 mg of ritonavir; MCP-1, monocyte chemoattractant protein-1; MHV, mouse hepatitis virus; NO, nitric oxide; NPPV, non-invasive positive pressure ventilation; R0, reproductive number; S protein, spike glycoprotein; SARS, severe acute respiratory syndrome; SARS-CoV, SARS-associated coronavirus; TGEV, transmissible gastroenteritis virus; TNF-α, tumour necrosis factor-α; WHO, World Health Organization.

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a previously unrecognized coronavirus as the aetiological agent of SARS. The virus was named SARS-CoV (SARS-associated coronavirus). The global outbreak ended in July 2003 with a total of 8098 probable cases and at least 774 deaths recorded (see http://www.who.int/csr/sars/country/table2003_09_23/en for a summary of probable SARS cases with onset of illness from 1 November to 31 July 2003).

THE VIRUS

The family Coronaviridae contains two separate genera: coronaviruses and toroviruses. Coronaviruses are found in a wide range of animal species. In humans, coronaviruses are mainly respiratory pathogens, although they have been occasionally shown to be the cause of some cases of diarrhea. Before the SARS epidemic, only two human coronaviruses had been characterized (HuCoV-229E and HuCoV-OC43). Both of these usually cause a mild upper respiratory tract infection.

Coronaviruses are large lipid-enveloped, positive-sense, single-stranded RNA viruses, approx. 30 kb in length and are the largest RNA viruses known. The virus codes for several proteins, including an RNA-dependent RNA polymerase (Pol), a surface spike glycoprotein (S protein), which attaches the virus to a host cell and is the target for neutralizing antibodies [8,9], a small envelope protein (E), a membrane glycoprotein (M) and a nucleocapsid protein (N) complexed with the viral RNA. The haemagglutinin esterase (HE) protein is also coded for in HuCoV-OC43 and some animal coronaviruses, but not in SARS-CoV [10]. There are other ORFs (open reading frames), whose functions are being gradually revealed. Coronaviruses have a unique replication system in that all mRNAs form a nested set with a common polyadenylated 3’-end fragment being translated into amino acids [11]. Mutations are common, as for all RNA viruses, and if two coronaviruses infect the same host cell simultaneously genetic recombination is possible [12]. However, no evidence of recombination was found from the SARS-CoV genomes detected during the course of global outbreak in 2003 [13,14].

Animal and human coronaviruses have been classified into three different serologically distinct groups based on their antigenicity [13,14]: Group 1 contains HuCoV-229E and porcine [TGEV (transmissible gastroenteritis virus) and PDEV, (porcine diarrhoea epidemic virus)], feline [FIPV (feline infectious peritonitis virus)] and canine coronaviruses; Group 2 contains HuCoV-OC43 along with MHV (mouse hepatitis virus), bovine coronavirus and haemagglutinating encephalomyelitis virus; and Group 3 contains avian coronaviruses, including IBV (infectious bronchitis virus) of chickens and turkey coronavirus. SARS-CoV seems to lie in a group of its own, based on sequencing studies of its various viral proteins [13,14].

The receptor for the human coronavirus HuCoV-229E has been reported to be human aminopeptidase N (CD13) [15]. In Group 2, HuCoV-OC43 may use one of several cell-surface molecules, including 9-O-acetylated neuraminic acid and the HLA-1 molecules [16,17]. It has been shown that SARS-CoV uses ACE-II (angiotensin-converting enzyme 2) as the cellular receptor [18,19]. A good correlation between the expression of ACE-II and tissue tropism has been shown [20]; however, the presence of ACE-II is unlikely to be the sole determinant for tropism [21]. The C-type lectin CD229L (L-SIGN) human cellular glycoprotein may also possibly be a receptor for SARS-CoV [22].

CLINICAL FEATURES

SARS-CoV produces an acute viral infection in humans with an incubation period ranging from 2–10 days [3–5]. During the 2003 outbreak, most patients were admitted to hospital between 3–5 days following the onset of illness [23]. The presenting features in adults are pronounced. These include persistent high fever, chills and rigor, malaise, myalgia, headache and dry cough. Most patients had some degree of dyspnoea at presentation, which increased towards the end of the first week of illness. Sputum production, sore throat and rhinorrhea were less commonly reported symptoms [3–5,24,25].

The reported proportion of patients with gastrointestinal symptoms varies among different clusters. For the first hospital outbreak in Hong Kong, 20 % of patient had diarrhoea at presentation, and another 18 % developed diarrhoea during the course of illness [26]. It is worth noting that in eight of the 138 (5.8 %) patients in the cohort, fever and diarrhoea were their only presenting symptoms. The diarrhoea was mainly watery without blood or mucus, lasting for $3.7 \pm 2.7$ days. A few patients had mild abdominal pain. In the Toronto outbreak, 24 % of the 144 patients had diarrhoea at presentation [3]. A remarkably high proportion (70 %) of patients in the rapidly evolving community outbreak, which occurred at the Amoy Gardens Residential Estate in Hong Kong, had diarrhoea at presentation.

Reactive hepatitis is a common complication of SARS-CoV infection with 24 % of patients having elevated ALT (alanine aminotransferase) levels on admission, and 69 % had raised ALT levels during the subsequent course of their illness. Those with severe hepatitis had worse clinical outcome [27].

Lymphopenia, low-grade disseminated intravascular coagulation (DIC—thrombocytopenia, prolonged activated partial thromboplastin time and elevated D-dimers), elevated LDH (lactate dehydrogenase) and CK (creatinine kinase) are common abnormalities detected in SARS patients [3–6,28,29].
In general, the radiographical features of SARS are similar to those found in community-acquired pneumonia caused by other organisms [30]. Nevertheless, several characteristic features are frequently observed in SARS, including the predominant involvement of the lung periphery and the lower zones, whereas cavitation, hilar lymphadenopathy and pleural effusion are rarely found [3,30]. Radiographical changes progress from a unilateral focal air-space opacity, to multifocal or bilateral involvement during the later phase of disease. These lesions resolve, naturally or as a response to treatment, in a large proportion of patients (Figure 1) [3,30]. In a case series, 12% of patients developed spontaneous pneumomediastinum and 20% of patients developed evidence of ARDS (acute respiratory distress syndrome) over a period of 3 weeks [31]. The reported incidence of barotrauma among patients receiving intensive care was high (26%), despite using low-volume and low-pressure mechanical ventilation [32]. High-resolution computer tomography of the thorax is useful in detecting lung opacities in cases with a high index of clinical suspicion of SARS, but with unrevealing unremarkable chest radiographs. Remarkable features observed from high-resolution computer tomography include ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening, with predominantly peripheral and lower lobe involvement (Figure 2) [33].

SARS-CoV was detected in the cerebrospinal fluid and serum samples of two cases with status epilepticus [34,35]. The data suggest that a severe acute neurological syndrome might occasionally accompany SARS.

Older subjects with SARS often show atypical presenting features such as decrease in general well-being, poor feeding and delirium [36–38]. The fact that older SARS patients might be afebrile further hinders early recognition. Young children (<12 years of age) often run a more benign clinical course mimicking other viral upper respiratory tract infections, whereas teenagers tend to have a clinical course similar to that of adult SARS patients [3,39]. No fatality has been reported in young children and teenage patients [39–42].

A number of studies have been conducted to search for asymptomatic cases of SARS-CoV infection [43,44]. It is now quite certain that asymptomatic infection is very rare in adults; however, data on children and elderly are less comprehensive.

TRANSMISSION

The origin of SARS-CoV is, at present, thought to be the Himalayan palm civet (Paguma larvata) found in Guangdong province in south China, from which coronaviruses very similar to SARS-CoV isolated from humans have been detected [45–47]. The fact that a much higher seroprevalence of SARS-CoV was found among wild animal handlers in Guangdong also supports its animal origin. Although it is still a mystery how SARS-CoV has crossed the species barrier, a number of reports have provided detailed descriptions on the transmission of SARS-CoV among humans.

The transmission of most respiratory viruses is a combination of direct contact (touch), short-range (large
High-resolution computer tomography of the thorax taken on day 7 of a patient with SARS

Several areas of ground-glass opacities involving predominantly the lower lobes of both lungs were observed.

Next, there was evidence to suggest that SARS might have spread by long-range airborne transmission in a major community outbreak in a private residential complex in Hong Kong [57]. There are several other hypotheses for this major outbreak, including passive carriage of viruses by pests, drying up of U-shaped bathroom floor drain which allowed the backflow of contaminated sewage or its aerosolized particles and creation of infectious aerosol current by the use of residential exhaust fans in the toilet [58,59]. Other circumstantial evidence are also in line with the airborne transmission hypothesis for SARS-CoV. For instances, air samples obtained from a room occupied by a SARS patient, and swabs taken from frequently touched surfaces in rooms and at a nurse station, were positive for SARS-CoV by PCR [60]. The temporal–spatial spread of SARS among patients in a medical ward where there was a SARS outbreak, at the Prince of Wales Hospital in Hong Kong, was also consistent with airborne transmission [61].

Hence, from this account, one of the main difficulties in controlling SARS transmission during the early stages of the worldwide epidemic is the readiness with which the virus could spread between healthcare workers and their patients (mainly direct or short-range transmission), but also the existence of ‘superspreaders’ who generate a far greater than average number of secondary cases. The reasons for this are still not known for certain, but may be a combination of host and viral factors.

The basic $R_0$ (reproductive number) of an infectious agent generally gives an indication of transmissibility of the agent and can also estimate the vaccine coverage required in an otherwise susceptible population, to prevent person-to-person spread of the agent and an ensuing epidemic. Estimates for the $R_0$ of SARS-CoV have been reported by several authors, but in each case, the superspreaders were left out of the estimates, so as not to skew the results for the majority of SARS-CoV-infected individuals. The $R_0$ for SARS-CoV has been estimated to be between 2 and 3 [62,63]. These two analyses excluded superspreading events in their final value of $R_0$, because the transmission route for these events were almost certainly atypical of the disease in most cases and may have been assisted in some way [57,61]. This value of $R_0$ puts SARS-CoV quite low down on the scale of transmissibility (Table 1) [64–66]. Thus, in the absence of superspreaders, the transmissibility of SARS-CoV would be lower than poliovirus.

**PATHOGENESIS**

After binding to their respective receptors, using the S protein, human coronaviruses (HuCoV-229E, HuCoV-OC43 and SARS-CoV) enter their host cell. This is usually a ciliated respiratory tract epithelial cell in the nasopharynx [12,67]. Thereafter, the mechanisms by which SARS-CoV causes disease can be separated into...
Table 1 \( R_0 \) for various infectious agents

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>Basic ( R_0 )</th>
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<tr>
<td>Measles</td>
<td>15–17</td>
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<tr>
<td>Whooping cough</td>
<td>15–17</td>
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<td>Mumps</td>
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<td>Rubella</td>
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<td>Diphtheria</td>
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<tr>
<td>Poliomyelitis</td>
<td>5–6</td>
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<tr>
<td>Influenza*</td>
<td>1.68–20</td>
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<tr>
<td>SARS†</td>
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Adapted from Mims et al. [64], with additional references: *[62,63]; †[65,66].

Table 1 \( R_0 \) for various infectious agents

![Image](http://portlandpress.com/clinsci/article-pdf/110/2/193/437670/cs1100193.pdf)

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two: (i) the direct lytic effects of the virus on host cells, and (ii) the host immune response to the infection.

The immune response to viral invasion and replication is a combination of early innate and later adaptive responses. Animal and in vitro studies have demonstrated that coronavirus replication within the host cell leads to a variety of effects, such as cellular necrosis or lysis [68,69], apoptosis [68,70] or cell fusion to form syncytia [71]. Studies in mice have shown that there is a potent CD8 T-cell response with acute MHV infection [72], and that fulminant hepatitis can result from induced transcription of a novel fgf2 prothrombinase gene by the MHV nucleocapsid protein [73]. In cats with FIPV, the humoral response and production of antibodies to the S protein induces peritonitis [74].

Human infection with SARS-CoV, similarly, leads to an acute inflammatory response. In humans, SARS-CoV causes diffuse alveolar damage and deposition of fibrin with macrophage and giant cell infiltration in lung tissue [75,76]. Acute hepatitis has been widely reported and may be a result of immune-mediated, rather than direct, SARS-CoV viral damage [27,77,78]. Haematological disturbances have been suspected to be a result of both direct viral and immune-mediated mechanisms affecting haematopoiesis [16]. The S protein may be the main factor in determining the severity of clinical disease, because of its roles in viral entry, pathogenesis, antiviral response, virulence and cellular and species tropism [8,20,45,79]. Again, studies on animal coronavirus S proteins have helped to define this. Mutations in S proteins have been shown to affect the viral virulence and tissue tropism of MHV [80,81] and TGEV [82].

Numerous authors have attempted to determine the role of various cytokines in the pathogenesis of SARS-CoV infection, but the picture is still confusing. Most reports describe a change in levels of IL (interleukin)-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-17 and IL-18, TNF-\( \alpha \) (tumour necrosis factor-\( \alpha \)) and IFN (interferon)-\( \gamma \) and -\( \alpha \), but there is little consistency between the different reports.

In one study from Hong Kong, 20 patients with proven SARS-CoV infection demonstrated raised levels of inflammatory cytokines IL-1, IL-6 and IL-12 and the neutrophil chemokine IL-8. The Th1 cytokine IFN-\( \gamma \) was also raised; however, the inflammatory cytokine TNF-\( \alpha \) was not and neither was the inflammatory cytokine IL-10, the Th1 cytokine IL-2 or the Th2 cytokine IL-4. The picture is one of Th1-cell-mediated immunity [83]. Other cytokines shown to be raised were MCP-1 (monocyte chemoattractant protein-1) and IP-10 (IFN-\( \gamma \)-inducible protein-10). Other authors have supported some of these findings. Duan et al. [77] investigated the cytokine profile in Beijing SARS patients with elevated liver enzymes and also reported raised levels of IL-1 (IL-\( \beta \)), IL-6 and IL-8, but also raised levels of IL-2, IL-4 and IL-10, in contrast with Wong et al. [83]. In fact, raised levels of IL-6 and IL-8 have also been reported from SARS patients in Guangzhou [84] and Taiwan [85]. Xie et al. [86] and Zhang et al. [87] report raised levels of IL-8 and IL-6 respectively. Some of these studies [77,87] and others [88] have also reported raised levels of IL-10.

However, contrasting results have also been reported between these authors. Zhang et al. [87] reported a fall in IL-8 levels, whereas Wang et al. [89] reported no change in levels. Similarly, Ng et al. [90] and Wang et al. [89] reported no change in IL-6 levels. With TNF-\( \alpha \), the picture is very mixed, with several reports stating an increase in levels [77,86,89], some reporting no significant elevation [83,87,90] and others reporting a fall in levels [85]. The picture for IFN-\( \gamma \) is equally inconsistent with Wong et al. [83] and Huang et al. [85] reporting a rise in levels, but Zhang et al. [87] reporting a fall.

The main picture that seems to emerge from the majority of the studies is that IL-6 and IL-8 are raised during SARS-CoV infection. IL-6 is secreted by macrophages and T-lymphocytes and causes fever, induces acute-phase proteins and activates lymphocytes. IL-8 is secreted by monocytes, macrophages, fibroblasts and keratinocytes and is a chemoattractant and enhances access for neutrophils to the site of infection [91]. The reported variations in the levels of all these inflammatory markers may well be because of differences in sample collection times relative to the onset of SARS-CoV infection. Generally, however, the reports agree that SARS-CoV infection produces a strong host immune response and that the complications of SARS may well be a consequence of this. Further studies are necessary to define the role of specific cytokines better, especially if they can lead to an earlier diagnosis or prognosis, or even a specific therapy for SARS [92].

**TREATMENT**

The clinical course of SARS can be divided into two phases: Phase I refers to active viral replication where patients experience high fever, myalgia and other systemic symptoms that generally improve after a few days; and
Phase II refers to the stage of immunopathological injury where patients experience a recurrence of fever, increasing hypoxaemia and radiological progression of pneumonia with falls in viral load. The timing of administration of treatment with respect to these two phases needs to be considered when evaluating its efficacy.

Ribavirin

Ribavirin, a nucleoside analogue that has activity against a number of viruses \textit{in vitro}, was widely used for treating SARS patients after observing the lack of clinical response to broad-spectrum antibiotics and oseltamivir \cite{3–6,31}. Nevertheless, it is now known that ribavirin has no significant \textit{in vitro} activity against SARS-CoV \cite{93–95}. Haemoglobin levels in approx. 60% of patients fell by 2 g/dl after 2 weeks of oral ribavirin therapy, at a dose of 1.2 g three times/day \cite{96}. The use of ribavirin for SARS in Toronto was based on the higher dosage used for treating haemorrhagic fever, which led to more toxicity, including elevated liver transaminases and brady-cardia \cite{5}. Furthermore, addition of ribavirin did not have any useful effect on the serum SARS-CoV viral load in paediatric SARS patients \cite{97}. Therefore it is highly 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 proteases \cite{13,14,98}. Lopinavir and ritonavir in combination is a boosted protease inhibitor regimen widely used in the treatment of HIV infection. \textit{In vitro} activity against SARS-CoV has been demonstrated for lopinavir and ribavirin at 4 and 50 µg/ml respectively. \textit{Inhibition} of \textit{in vitro} cytopathic effects was achieved down to a concentration of 1 µg/ml lopinavir combined with 6.25 µg/ml ribavirin. The data, therefore, suggest that this combination might be synergistic against SARS-CoV \textit{in vivo} \cite{99}. The addition of LPV/r (400 mg of lopinavir/100 mg of ritonavir) as initial therapy was associated with significant reduction in overall death rate (2.3 % compared with 15.6 %) and intubation rate (0 % compared with 11 %) when compared with a matched historical cohort that received ribavirin alone as the initial antiviral therapy \cite{100}. Other reported beneficial effects include a reduction in corticosteroid use, fewer nosocomial infections, a decreasing viral load and rising peripheral lymphocyte count \cite{99}.

In contrast, the subgroup that had received LPV/r as rescue therapy after receiving pulsed methylprednisolone treatment for worsening respiratory symptoms was not better than the matched cohort \cite{100}. The improved clinical outcome in patients that received LPV/r as part of the initial therapy may be due to the fact that both peak (9.6 µg/ml) and trough (5.5 µg/ml) serum concentrations of lopinavir could inhibit the virus \cite{101}. Nelfinavir, another protease inhibitor commonly used for HIV infection, has been shown to inhibit replication of SARS-CoV in Vero cell culture \cite{102}. Further evaluation of this form of therapy is warranted.

IFNs

Type I IFNs such as IFN-α are produced early as part of the innate immune response to virus infections. Type I IFNs inhibit a wide range of RNA and DNA viruses including SARS CoV \textit{in vitro} \cite{94,95,103}. Complete inhibition of cytopathic effects of SARS-CoV in culture was observed for IFN subtypes β-1b, α-n1 and α-n3, and human leucocyte IFN-α \cite{94}. IFN-α had an inhibitory effect \textit{in vitro} on SARS-CoV starting at concentrations of 1000 IU/ml (where IU is international units) \cite{95}, whereas recombinant human IFN-β1a potently inhibited SARS-CoV \textit{in vitro} \cite{104}. IFN-β and IFN-γ can synergistically inhibit the replication of SARS-CoV \textit{in vitro} \cite{105}. 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 \cite{106}, and combinations of ribavirin with either IFN-β or IFN-α also show synergistic effects \textit{in vitro} \cite{107}.

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 post-exposure treatment with pegylated IFN-α yielded intermediate results \cite{108}. Use of IFN-α 1 plus corticosteroids was associated with improved oxygen saturation, more rapid resolution of radiographical lung opacities and lower levels of CPK (creatine kinase) in SARS patients \cite{109}. These findings support clinical testing of approved IFNs for the treatment of SARS.

huMab (human monoclonal antibody)

There is evidence that SARS-CoV infection is initiated through binding of the SARS-CoV S protein to ACE-II \cite{18}. A high-affinity huMab has been identified against the SARS-CoV S protein, termed 80R, that has potent neutralizing activity \textit{in vitro} and \textit{in vivo} \cite{110}. huMab 80R efficiently neutralizes SARS-CoV and inhibits syncytia formation between cells expressing the S protein and those expressing the SARS-CoV receptor ACE-II. huMab 80R may be a useful viral entry inhibitor for the emergency prophylaxis and treatment of SARS \cite{110}. huMab has been 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 \cite{111}.

Vaccines

Currently, different vaccines, such as whole-killed vaccine, adenovirus vector vaccine and recombinant S
protein vaccine, are being tested. An adenoviral-based vaccine has been shown to induce strong SARS-CoV-specific immune responses in rhesus macaques and hold promise for the development of a protective vaccine against SARS-CoV [115]. A DNA vaccine based on the S gene has been shown to induce the production of a specific IgG antibody against SARS-CoV efficiently in mice with a seroconversion rate of 75% after three doses of immunization [113, 114]. Recombinant S proteins that exhibit antigenicity and receptor-binding ability are also good candidates for developing a SARS vaccine [115]. It has been shown that a recombinant attenuated vaccinia virus, Ankara, expressing the S protein of SARS-CoV can elicit protective immunity in mice [116]. Another recombinant attenuated parainfluenza virus expressing the S protein also produced immunity following intranasal inoculation to mice [117]. A synthetic peptide derived from the S protein is another target for vaccine development. Promising results have been obtained in vitro [118] and in vivo from rabbit and monkey models [119].

**Systemic corticosteroids**

During the Phase II of clinical course when patients progressed to develop pneumonia and hypoxaemia, intravenous administration of rescue-pulsed methylprednisolone has been shown to suppress cytokine-induced lung injury [3, 31, 96, 99, 120]. The rationale could be that the progression of the pulmonary disease is mediated by the host inflammatory response [31]. Corticosteroids significantly reduced IL-8, MCP-1 and IP-10 concentrations from 5–8 days after treatment in 20 adult SARS patients [81]. Induction of IP-10 is thought to be a critical event in the initiation of immune-mediated lung injury and lymphocyte apoptosis [82].

The use of rescue-pulsed methylprednisolone during clinical progression was associated with favourable clinical improvement, with resolution of fever and lung opacities within 2 weeks [3, 31, 96, 120]. However, a retrospective analysis showed that the use of pulsed methylprednisolone was associated with increased risk of 30 day mortality (adjusted odds ratio, 26.0; 95% confidence interval, 4.4–154.8) [121]. This retrospective study could not establish whether a causal relationship existed between the use of methylprednisolone and an increased risk of death, as clinicians were more inclined to give pulsed methylprednisolone therapy in deteriorating patients. Nevertheless, complications, such as disseminated fungal disease [122] and avascular necrosis of bone, have been reported following corticosteroid therapy [123]. With the rescue pulsed steroid approach, avascular necrosis of bone was found in 12 (4.7%) patients after screening 254 using MTI (magnetic resonance imaging). The risk of avascular necrosis was 0.6% for patients receiving <3 g, and was 13% for those receiving >3 g of prednisolone-equivalent dose [124]. A randomized placebo-controlled study conducted at Prince of Wales Hospital, Hong Kong showed that plasma SARS-CoV RNA concentrations in the second and third weeks of illness were higher in patients given initial hydrocortisone (n=10) than those given normal saline (n=7) during Phase I of the clinical course of illness [125]. Despite the small sample size, the data suggest that pulsed steroid given in the earlier phase may prolong viraemia and thus it should only be given during later phase for rescue purpose. Carefully designed clinical trials, if ever possible, of a larger sample size are required to determine the optimal timing and dosage of systemic steroid in the treatment of the possibly immune-mediated lung injury in SARS.

**Convalescent plasma**

Convalescent plasma, donated by patients who had recovered from SARS, contains neutralizing antibodies and may be used clinically for treating other SARS patients [126, 127]. Research work in the preparation of SARS-CoV-specific hyperIg from convalescent plasma donated by patients who have recovered from SARS is currently in progress.

**Traditional Chinese medicine**

Glycyrrhizin, an active component of liquorice roots, has been shown to inhibit the replication of SARS-CoV in vitro [93]. A controlled study comparing integrative Chinese and Western medicine compared with Western medicine alone has suggested that the combination treatment given in the Phase I of SARS was more effective in reducing the number of patients with abnormal oxygen saturation [128]. However, it was not clear which of the Chinese medicine components was responsible for the benefit, and the dosage of steroid given to both groups was not clear.

**IVIg (intravenous γ-globulin) and pentaglobulin**

IVIg has immunomodulatory properties and may downregulate cytokine expression [129], and was used quite 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-mass heparin [54]. There was evidence of pulmonary embolism in four out of eight postmortem cases [130]. In addition, there were five cases of large artery ischaemic stroke of which three cases had been given IVIg [131].

Pentaglobulin is IgM-enriched Ig. It 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 radiographical scores. It was difficult to judge its effects, as the study was uncontrolled and pulsed steroid
was also used concurrently [132]. Pulmonary artery thrombosis has been reported in a patient with SARS who was treated with ribavirin, steroid, lopinavir/ritonavir, IVIg and pentaglobulin [133]. It is possible that the IVIg- or pentaglobulin-induced increase in viscosity may be consequential in patients with hypercoagulable states such as SARS [134].

**NO (nitric oxide)**

Inhaled NO has been 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. Interestingly, the beneficial effects persisted after termination of NO inhalation [135]. NO has been shown to inhibit the replication cycle of SARS-CoV in vitro [136].

**NPPV (non-invasive positive pressure ventilation)**

Approx. 20 % of SARS patients developed ARDS requiring invasive mechanical ventilation and this incurred a huge demand on intensive care units. Performing endotracheal intubation is a known risk for acquiring SARS-CoV from the patient [137]. NPPV via face mask was applied to 20 patients in a hospital ward in Hong Kong which was installed with double exhaust fans and full personal protective equipment. Intubation was avoided in 14 patients and none of the 105 healthcare workers developed SARS clinically. SARS-CoV serology was negative in 102 (97 %), whereas the other three refused blood tests [138]. Although one cannot completely eliminate the possibility of subclinical SARS, it appears that NPPV is safe when applied in a ward environment with adequate air exchange provided the healthcare workers are well-equipped with full personal protective equipment and observe strict contact and droplet precautions [139]. Careful evaluation of the effectiveness of these possible modalities is needed before they can be recommended for treatment.

**OUTCOMES**

**Short-term outcome**

Based on the data received by the WHO (http://www.who.int/csr/sars/archive/2003_05_07a/en/print.html), the case fatality rate for SARS was < 1 % for patients aged 24 years or younger, 6 % for 25–44 years, 15 % for 45–64 years, and > 50 % for patients aged 65 years or older. There is no evidence to suggest that a difference in mortality rate exists between different ethnic groups. A number of clinical/laboratory parameters have been shown have a prognostic value. Poor prognostic factors include advanced age [3,23,31,141], chronic hepatitis B treated with lamivudine [31], severe hepatitis [27], high initial LDH [141], high peak LDH [3], high neutrophil count on presentation [3,141], diabetes mellitus or other co-morbid conditions [5,142], low CD4 and CD8 lymphocyte counts at presentation [143] and a high initial SARS-CoV viral load [97,144].

**Long-term outcome**

Significant impairment of diffusing capacity occurred in 15.5 and 23.7 % of SARS survivors at the Prince of Wales Hospital cohort at 6 and 12 months respectively [145,146]. Although significant improvement in serial chest radiography was observed among the SARS survivors, 27.8 % of them still had abnormal radiographical scores at 12 months [146]. Despite the presence of extensive parenchymal changes revealed by computer tomography during the early convalescent period, surprisingly most SARS survivors had lung function test indices within normal limits. However, their exercise ability (6 min walk distance) at 12 months after illness onset was remarkably lower than the general population [146]. The functional disability appears out of proportion to the degree of lung function impairment and may be due to extrapulmonary factors such as muscle de-conditioning and steroid myopathy [145,146]. Critical-illness-associated polyneuropathy/myopathy has also been observed in a few SARS survivors [147]. The reported incidence rates of avascular necrosis of bone among different cohorts in Hong Kong range from 4.7–15 % [124,148,149], whereas one study from Beijing reported a high incidence of 42 % [123].

In addition, there was significant impairment of health-related quality of life in our patients at 6 and 12 months [145,146]. The results are not surprising as, in addition to the physical impairment, the long period of isolation and extreme uncertainty during the SARS illness had created enormous psychological stress [150] and mood disturbances [151]. Furthermore, steroid toxicity, personal vulnerability and psychosocial stressors might have contributed to the development of psychosis in some patients [152]. Longer term follow-up is needed to assess if these deficits are persistent.

**SUMMARY AND CONCLUSIONS**

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. Healthcare workers are particularly vulnerable to SARS as the viral load of SARS-CoV in patients increase to peak levels during the second week when patients are hospitalized [21,31]. Since there is currently no proven effective treatment for 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 and eye protection) for healthcare workers managing SARS patients, avoid using nebulizers on general wards [3,51], contact tracing and quarantine isolation for close contacts are all important measures in controlling the spread of the infection in hospital and community.

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