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An overview on Severe Acute Respiratory Syndrome (SARS)

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ABSTRACT: ***An overview on Severe Acute Respiratory Syndrome (SARS). D.S.C. Hui.***

Severe acute respiratory syndrome (SARS) is a newly emerged infectious disease that has caught the medical profession by surprise in 2003. The major clinical features include persistent fever, chills/rigor, myalgia, malaise, dry cough, headache and dyspnoea but diarrhea occurs in 40-70% of patients after hospital admission. Respiratory failure is the major complication of SARS; at least half of the patients require supplemental oxygen during the acute phase whereas about 20% of patients progress to acute respiratory distress syndrome requiring invasive mechanical ventilatory support. In contrast, the severity is generally mild in infected young children.

Due to our limited understanding of this new disease, treatment of SARS was empirical in 2003. Protease inhibitor (Lopinavir/ritonavir) in combination with ribavirin may play a role as antiviral therapy in the early phase whereas nelfinavir is a promising alternative. The role of interferon and systemic steroid in preventing immune-mediated lung injury deserves further investigation. In addition, other anti-viral treatment, RNA interference, monoclonal antibody, synthetic peptides, and vaccines are being developed. Rapid diagnosis, early isolation, and good infection control measures are important in preventing spread of the infection.

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Introduction

The rapid emergence of severe acute respiratory syndrome (SARS) in 2003 caught the medical profession by surprise 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]. A novel coronavirus (CoV) is responsible for SARS [6-10], and the genome sequence of the SARS-CoV is not closely related to any of the previously characterized coronaviruses [11-13]. In this article, the epidemiology, clinical presentation, and the possible therapeutic agents are reviewed.

Epidemiology

In Nov 2002, there was an unusual epidemic of severe pneumonia of unknown aetiology in Foshan, Guangdong Province in southern China, with a high rate of transmission to healthcare workers (HCWs) [14,15]. A retrospective analysis of 55 patients admitted to a chest hospital with atypical pneumonia in Guangzhou between Jan 24 and Feb 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 shared the same origin with those in other countries, with a phylogenetic pathway that matched the spread of SARS to other parts of the world [16].

SARS-CoV appears to have originated from wild animal reservoir in mainland China because masked palm civets (Paguma larvata) and the raccoon dog (Nyctereutes procyonoides) had a CoV almost identical to that in SARS patients. There was also a much higher sero-prevalence of SARS-CoV among wild animal handlers than controls in Guangdong [17, 18].

A 64-year old physician from southern China, who had visited HK on 21 Feb 2003 and died ten days later of severe pneumonia, was the source of infection causing subsequent outbreaks of SARS in HK [1, 19]. Vietnam, Singapore [2] and Canada [3]. 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 was staying in HK. Through international air travel, these visitors spread the infection globally within a short period.

SARS appears to spread by close person-to-person contact via droplet transmission or fomite [20]. The high infectivity of this viral illness is reflected by the fact that 138 patients (many of whom being HCWs) were hospitalized with SARS within 2 weeks as a result of exposure to one single patient (a visitor of Hotel M), who was admitted with community acquired pneumonia (CAP),

on a general medical ward at the Prince of Wales Hospital (PWH)in HK [1, 21]. This super-spreading event was thought to be related to the use of nebulized bronchodilator for its muco-ciliary clearance effect to the index case together with overcrowding and poor ventilation in the hospital ward [1, 21]. SARS-CoV was also detected in tears, and this might be another source of spread among HCWs and inoculating patients [22]. In addition, there was evidence to suggest that SARS might have spread by airborne transmission in a major community outbreak in a private residential complex in HK [23]. There are several other hypotheses for this major outbreak including passive carriage of virus by pests, drying up of U shaped bathroom floor drain, and faecal-oral viral loading through contaminated surfaces as a result of the chimney effects created by the use of exhaust fans in the presence of blockage of the contaminated sewage system [24, 25]. There are however additional data in support of SARS having the potential of being converted from droplet to airborne droplet transmission. 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 PCR testing [26]. The temporal-spatial spread of SARS among inpatients in the index medical ward of the PWH in HK was also consistent with airborne transmission [27]. These data emphasize the need for adequate respiratory protection in addition to strict contact and droplet precautions.

Clinical and laboratory features

The estimated mean incubation period was 4.6 days (95% CI, 3.8 to 5.8 days) whereas the mean time from symptom onset to hospitalization varied between 2 and 8 days, decreasing over the course of the epidemic. The mean time from onset to death was 23.7 days (CI, 22.0 to 25.3 days), whereas the mean time from onset to discharge was 26.5 days (CI, 25.8 to 27.2 days) [28]. The major clinical features on presentation include persistent fever, chills/rigor, myalgia, dry cough, headache, malaise and dyspnoea. Sputum production, sore throat, coryza, nausea and vomiting, dizziness and diarrhea are relatively less common features [1-4, 29].

Watery diarrhea became a prominent extrapulmonary symptom in 40-70% of patients with SARS one week down the clinical course of the illness [30, 31]. 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 both the small and large intestines [31]. Reactive hepatitis is a common complication of SARS-CoV infection with 24% and 69% of patients respectively having elevated alanine aminotransferase (ALT) on admission and during the subsequent course of the illness. Those with severe hepatitis had worse clinical outcome but chronic hepatitis B itself was not associated with worse clinical outcome [32].

SARS-CoV was detected in the cerebrospinal fluid and serum samples of two cases with status epilepticus [33, 34]. The data suggest that a severe acute neurologic syndrome might occasionally accompany SARS.

Older subjects may have atypical presentation such as decrease in general well-being, poor feeding, fall/ fracture [35], and in some cases, delirium, without the typical febrile response (temperature > 38C) [35-37]. In contrast, young children (< 12 years of age) often run a more benign clinical course mimicking other viral upper respiratory tract infections whereas some teenagers tend to have a clinical course similar to those of adult SARS patients [1, 38]. There was no reported fatality in young children and teenage patients [38-41].

The clinical course of SARS generally follows a typical pattern [30]: Phase 1 (viral replication) is associated with increasing viral load and clinically characterized by fever, myalgia, and other systemic symptoms that generally improve after a few days; Phase 2 (immunopathological injury) is characterized by recurrence of fever, hypoxaemia, and radiological progression of pneumonia with falls 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 above 90% [42] whereas about 20% of patients would progress into acute respiratory distress syndrome (ARDS) necessitating invasive ventilatory support [30]. Peiris et al [30] have shown progressive decrease in rates of viral shedding from nasophargynx, stool, and urine from day 10 to day 21 after symptom onset in the 20 patients who had serial measurements with RT-PCR. Thus clinical worsening during phase 2 is most likely the result of immune-mediated lung injury due to an over-exuberant host response and cannot be explained by uncontrolled viral replication [30].

Lymphopenia, low grade disseminated intravascular coagulation (thrombocytopenia, prolonged activated partial thromboplastin time, elevated D-Dimer), elevated lactate dehydrogenase (LDH), and creatinine kinase (CPK) are common laboratory features of SARS [1-3, 19, 43, 44]. Absolute lymphopenia occurs in 98% of cases of SARS during the clinical course of the disease. The CD4 and CD8 T lymphocyte counts fall early in the course of SARS, whereas low counts of CD4 and CD8 at presentation are associated with adverse clinical outcome [45]. The CD3 and CD4 T cell percentages have been reported to be negatively correlated with the appearance of IgG antibody against SARS-CoV [46]. However a retrospective study in Toronto has shown that all laboratory variables except absolute neutrophil count demonstrated fair to poor discriminatory ability in distinguishing SARS from other causes of CAP. Routine laboratory tests including the absolute lymphocyte count may not be reliable in the diagnosis of SARS [47].

Radiographic features of SARS resemble those found in other causes of CAP [48]. 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, 48]. Radiographic progression from unilateral focal air-space opacity to either multi-focal or bilateral involvement during the second phase of the disease, followed by radiographic improvement with treatment, is commonly observed [1, 48]. In a case series, 12% of patients developed spontaneous pneumo-mediastinum and 20% of patients developed evidence of ARDS over a period of 3 weeks [30]. The incidence of barotrauma (26%) in ICU admissions is high despite low volume and low pressure mechanical ventilation [49]. HRCT of thorax is useful in detecting lung opacities in cases with a high index of clinical suspicion of SARS but unremarkable chest radiographs. Common HRCT features include ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening, with predominantly a peripheral and lower lobe involvement [50].

Laboratory Diagnosis

The detection rates for SARS CoV using conventional reverse transcriptase polymerase chain reaction (RT-PCR) are generally low in the first week of illness whereas serology for confirmation may take 28 days to reach a detection rate above 90% [30]. By optimizing RNA extraction methods and applying quantitative real-time RT-PCR techniques, the sensitivity of NPA specimens for early diagnosis of SARS can be enhanced to 80% for the first 3 days [51]. Quantitative measurement of blood SARS-CoV RNA with real-time RT-PCR technique has a detection rate close to 80% during the first week of illness but the detection rates drop to 75% and 42% on day 7 and day 14 respectively (table 1) [52-54].

Table 1. - Laboratory diagnostic tests for SARS [30, 51-54]

RT-PCR	**Detection rate**
Nasopharyngeal aspirate	32% Day 3, 68% Day 14 (conventional RTPCR). 80% with real-time quantitative RTPCR assay during first 3 days.
Stool	97% Day 14
Urine	42% Day 15
Real-time quantitative Serum SARS-CoV RNA	80% Day 1, 75% Day 7, 45% Day 14
Serology IgG seroconversion to SARS- CoV	15% Day15 60% Day 21 >90% Day 28

Treatment

Due to limited knowledge of this newly emerged disease, empirical treatment was given during the SARS outbreak in 2003. Because of the unexpected acute medical crisis with many HCWs getting infected in 2003, it was difficult to conduct randomized placebo-controlled trial of sufficient sample size evaluating treatment for SARS.

Ribavirin

Ribavirin, a nucleoside analogue that has activity against a number of viruses in-vitro, was widely used in the treatment of SARS in 2003 following lack of clinical response to broad-spectrum antibiotics and oseltamivir [1-3, 19, 30]. Nevertheless, ribavirin has no significant in-vitro activity against SARS-CoV [55-57]. About 60% of patients dropped the haemoglobin by 2g/dl after taking 2 weeks of oral ribavirin at 1.2 g tid [58]. The use of ribavirin for SARS in Toronto was based on a higher dosage for treating haemorrhagic fever virus, and led to more toxicity, including elevated transaminases and bradycardia [3]. Furthermore, addition of ribavirin did not have any favorable influence on the serum viral load of paediatric SARS patients [53]. 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 types of enzymatic targets including the proteases [11, 12, 59]. Lopinavir and ritonavir in combination is a boosted protease inhibitor widely used in the treatment of Human Immunodeficiency Virus (HIV) infection. In-vitro activity against SARS-CoV has been demonstrated for lopinavir and ribavirin at 4 ug/ml at 50 ug/ml respectively after 48 hours of incubation. Cytopathic inhibition was achieved down to a concentration of lopinavir 1 ug/ml combined with 6.25 ug/ml of ribavirin and the data suggested that this combination might be synergistic against SARS-CoV *in vivo* [60]. 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%) when compared with a matched historical cohort that received ribavirin alone as initial anti-viral therapy [61]. Other beneficial effects included a reduction in corticosteroid use, less nosocomial infections, a decreasing viral load and rising peripheral lymphocyte count [60]. In contrast, the subgroup that had received LPV/r as rescue therapy after receiving pulse methylprednisolone (MP) treatment for worsening respiratory symptoms was no better than the matched cohort, and received a higher mean dose of MP [61]. 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 ug/ml) and trough (5.5 ug/ml) serum concentrations of lopinavir could inhibit the

virus [62]. Nelfinavir, another protease inhibitor commonly used for HIV infection, has been shown to inhibit replication of SARS-CoV in Vero cell culture [63]. Further evaluation of this form of therapy is warranted.

Interferons (IFN's)

Type I IFN's such as IFN-α are produced early as part of the innate immune response to virus infections. Type I IFN's inhibit a wide range of RNA and DNA viruses including SARS CoV *in vitro* [56, 57, 64]. Complete inhibition of cytopathic effects of SARS-CoV in culture was observed for IFN subtypes, β-1b, α-n1, α-n3, and human leukocyte IFN-α [56]. IFN-α showed an in vitro inhibitory effect on SARS-CoV starting at concentrations of 1000 IU/mL [57] whereas recombinant human IFN-β 1a potently inhibited SARS-CoV in vitro [65]. IFN β and IFN γ can synergistically inhibit replication of SARS-CoV in vitro [66]. 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 [67], whereas combinations of ribavirin with either IFN β1a or IFN α also show synergistic effects in vitro [68].

In experimentally infected cynomolgus macaques with SARS-CoV, 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 [69]. Use of IFN alfacon-1 plus corticosteroids was associated with improved oxygen saturation, more rapid resolution of radiographic lung opacities and lower levels of CPK in SARS patients [70]. These findings support clinical testing of approved IFN's for the treatment of SARS.

Human monoclonal antibody (HuMab)

There is evidence that SARS-CoV infection is initiated through binding of S1 protein to the angiotensin-converting enzyme 2 (ACE2) receptor [71]. A high-affinity human monoclonal antibody (huMab) has been identified against the SARS-CoV S1 protein termed 80R that has potent neutralizing activity *in vitro* and *in vivo* [72]. HuMab 80R efficiently neutralizes SARS-CoV and inhibits 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 [72]. Human monoclonal antibody could prophylactically reduce replication of SARS-CoV in the lungs of infected ferrets and abolish shedding of virus in pharyngeal secretions in addition to completely preventing SARS-CoV induced macroscopic lung pathology [73].

Vaccines

SARS-CoV is an enveloped RNA virus which contains several structural proteins. Currently, different vaccines such as whole killed vaccine, adenovirus vector vaccine, and recombinant spike protein vaccine are being tested. An adenoviral-based vaccine can induce strong SARS-CoV specific immune responses in rhesus macaques, and hold promise for development of a protective vaccine against SARS-CoV [74]. The spike (S) gene DNA candidate vaccine could induce the production of specific IgG antibody against SARS-CoV efficiently in mice with seroconversion ratio of 75% after 3 doses of immunization [75], whereas gene-based vaccination for the SARS-CoV elicits effective immune responses that generate protective immunity in mice [76]. Recombinant S protein exhibited the antigenicity and receptor-binding ability, and it could be a good candidate for further developing SARS vaccine [77]. Bisht et al have shown that recombinant forms of the highly attenuated modified vaccinia virus Ankara containing the gene encoding full-length SARS-CoV S protectively immunizes mice [78]. Another promising vaccine protects against infection in Monkeys when delivered intranasally [79].

Synthetic peptides can elicit specific antibodies to SARS-CoV in rabbits and monkeys [80], and peptides derived from the membrane-proximal (HR2) heptad repeat region of the spike protein have been shown to have inhibition against SARS-CoV in Vero cells [81]. The synthetic-peptide-based approach provides further insight for the future development of SARS vaccine.

Passive immunization as a treatment for SARS is also being investigated. Mouse and human antibodies against SARS can prevent infection in uninfected mice [82, 83].

Systemic corticosteroids

During phase 2 of SARS when there was progression of pneumonia and hypoxemia, intravenous rescue pulse MP was given to suppress cytokine-induced lung injury [1, 30, 58, 60, 84], with the rationale that progression of the pulmonary disease may be mediated by the host inflammatory response [30]. Corticosteroids significantly reduced interleukin-8 (IL-8), monocyte chemoattractant protein-1(MCP-1), and IFN-γ inducible protein -10 (IP-10) concentrations from 5 to 8 days after treatment in 20 adult SARS patients [85]. Induction of IP-10 is a critical event in the initiation of immune-mediated lung injury and lymphocyte apoptosis during the development of SARS whereas the prompt elevation of IL-6, IL-8 and MCP-1 is a sign of superinfection [86]. The use of rescue pulse MP during clinical progression was associated with favorable clinical improvement with resolution of fever and lung opacities within 2 weeks [1, 58]. However, a retrospective analysis showed that the use of pulsed MP was associated with increased risk of 30-day mortality (adjusted OR 26.0, 95% CI 4.4 to 154.8) [87]. This retrospective study could not establish whether a causal relationship existed between use and increased risk of death, and clinicians were more inclined to give pulsed MP therapy in deteriorating patients. Nev-

ertheless, complications such as disseminated fungal disease [88] and avascular necrosis of bones (AVN) [89] have been reported following prolonged corticosteroid therapy. With the rescue pulse steroid approach, the prevalence of AVN at the PWH cohort was 12 (4.7%) after screening 254 patients with magnetic resonance imaging. The risk of AVN was 0.6% for patients receiving < 3 g and 13% for those receiving > 3 g prednisolone-equivalent dose [90]. A randomized placebo controlled study conducted at PWH during the last part of SARS in HK has shown 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 1 of the disease [91]. Despite the small sample size, the data suggest that pulse steroid given in phase one may prolong viraemia and thus it should only be given during phase two for rescue purpose [91]. Carefully designed clinical trials of a larger sample size are required to determine the timing and dosage of systemic steroid in the treatment of the possible immune-mediated lung injury in SARS.

Convalescent plasma

Convalescent plasma, donated by patients who had recovered from SARS, contains neutralizing antibody and it may be clinically useful for treating other SARS patients [92, 93]. Research work in the preparation of SARS-CoV specific hyperimmune globulin from convalescent plasma donated by patients recovered from SARS is currently in progress.

Traditional Chinese Medicine

Glycyrrhizin, an active component of liquorice roots, and baicalin were active in inhibiting SARS-CoV in vitro but there are no clinical data in vivo [55, 68]. A controlled study comparing integrative Chinese and Western Medicine versus Western Medicine alone has suggested that the combination treatment given in phase one of SARS was more effective in reducing the number of patients with abnormal oxygen saturation [94]. However it was not clear which herbal compounds were responsible for the benefit and the dosage of steroid given to both groups was not clear.

RNA interference (RNAi)

RNAi is a recently discovered antiviral mechanism in plant and animal cells that induces a specific degradation of double-stranded RNA. Chemically synthesized siRNA duplexes targeting at both SARS-CoV genome sequence and open-reading frame levels are potent agents for inhibition of the viral infection and replication [95]. Other investigators have shown that siRNAs directed against Spike sequences and the 3'-UTR can inhibit replication of SARS-CoV in Vero-E6 cells [96]. The use of siRNAs in rhesus macaque provided relief from SARS-CoV infection induced fever and reduced both the SARS-CoV viral levels and acute diffuse alveolar damage [97].

Intravenous gammaglobulin (IVIg) & pentaglobulin

IVIg has immuno-modulatory properties and may down-regulate cytokine expression [98] IVIg was used quite extensively in Singapore during the SARS outbreak in 2003. However, it was noted that one third of critically ill patients in a hospital developed venous thrombo-embolism including pulmonary embolism despite prophylactic use of low molecular weight heparin [99]. There was evidence of pulmonary embolism in 4 out of 8 post-mortem cases [100]. In addition, there were 5 cases of large artery ischaemic stroke of which 3 cases had been given IVIg [101].

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 as the study was uncontrolled and pulsed steroid was also used concurrently [102]. Pulmonary artery thrombosis has been reported in a patient with SARS who was treated with ribavirin, steroid, kaletra, IVIg and pentaglobulin [103]. It is possible that IVIg or pentaglobulin-induced increase in viscosity may be consequential in patients with hypercoagulable states such as SARS [104].

Nitric oxide (NO)

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 [105]. NO has been shown to inhibit the replication cycle of SARS-CoV in vitro [106].

Non-invasive positive pressure ventilation (NPPV)

About 20% of SARS patients developed ARDS requiring invasive mechanical ventilation and this incurred a huge demand on ICU support in 2003. There was a significant association between endotracheal intubation and the development of nosocomial SARS among HCWs especially among the nurses who were closely looking after the patients [107]. NPPV via face mask was applied to 20 patients with SARS in a hospital ward in HK installed with good air exchange, stringent infection control measures, and full personal protective equipment (PPE). Intubation was avoided in 14 patients and none of the 105 HCWs involved developed SARS clinically. SARS-CoV serology was negative in 102 (97%) HCWs whereas the other 3 refused blood tests [108]. Although one cannot completely eliminate the possibility of sub-

clinical SARS, it appears that NPPV is safe when applied in a ward environment with adequate air exchange provided the HCWs are well equipped with full PPE and observe strict contact and droplet precautions [109].

Careful evaluation of the effectiveness of these possible modalities (table 2) is needed before they can be recommended for treatment.

Outcome

Short-term

The poor prognostic factors associated with a poor outcome (ICU admission or death) include advanced age [1, 28, 30, 110], male sex [28] atypical symptoms at presentation [28], chronic hepatitis B treated with lamivudine [30], severe hepatitis [32], high initial LDH [110], high peak LDH [1] high neutrophil count on presentation [1, 110] diabetes mellitus or other co-morbid conditions [3, 28, 111] low CD4 and CD8 lymphocyte counts at presentation [45], and a high initial SARS-CoV viral load [52, 112].

Long-term

Significant impairment of diffusing capacity (DLCO) occurred in 15.5% and 23.7% of SARS survivors at the PWH cohort at 6 and 12 months respectively [113, 114] whereas 27.8% of SARS survivors at the PWH cohort still had abnormal radiographic scores at 12 months although their serial CXRs showed significant improvement [114]. Despite the presence of extensive parenchymal changes on CT during the early convalescent period, most of the lung function test indices of SARS patients were surprisingly within normal limits in the majority of patients. Their exercise ability (6 min-walk distance) was remarkably lower than the general population at 12 months after illness onset [114]. The functional disability appears out of proportion to the degree of lung function impairment and may be due to extrapulmonary factors such as muscle deconditioning and steroid myopathy [113, 114]. Critical-illness associated polyneuropathy/mypoathy has also been observed in SARS survivors [115].

Table 2. - Potential modalities for the treatment of SARS

Ribavirin
Protease inhibitors (lopinavir/ritonavir or nelfinavir)
Interferons
Human monoclonal antibody
Vaccines
Convalescent plasma
Herbal compounds (glycyrrhizin, baicalin)
RNA interference (RNAi)
Intravenous gammaglobulin (IVIg) & pentaglobulin
Nitric oxide
Systemic corticosteroids

In addition, there was significant impairment of health status in most SF36 domains among our patients at 6 and 12 months [113, 114]. 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 [116] and mood disturbances [117]. In addition, steroid toxicity, personal vulnerability, and psychosocial stressors might have jointly contributed to the development of psychosis in some patients [118]. Longer term follow-up is needed to assess if these deficits are persistent.

AVN of bones has been reported from 4.7% to 15% in several different cohorts [90, 119, 120] in HK but one study in Beijing has reported a high prevalence of 42% [89].

Conclusions

SARS is a highly infectious disease with a significant morbidity and mortality. HCWs are particularly vulnerable to SARS as the viral load of SARS-CoV in patients increases to peak levels on day 10 of the illness [30]. Prevention of spread is most important in controlling this highly infectious disease. Since there is no proven effective treatment for SARS at present, early recognition, isolation and stringent infection control measures are the keys to control this highly contagious disease. Isolation facilities, strict droplet and contact precautions (hand hygiene, gown, gloves, N95 masks, eye protection) among HCWs managing SARS patients, avoidance of the use of nebulizer on general ward [1, 21], contact tracing, and quarantine isolation for close contacts are all important measures in controlling the spread of the infection in the hospital and the community.

Due to lack of large scale randomized, placebo-controlled data, the treatment of SARS for different clinical stages remains unclear. Protease inhibitor (Lopinavir/ritonavir or nelfinavir) in combination with ribavirin may play a role in the early phase whereas the role of interferon and systemic steroid in preventing immune-mediated lung injury needs further investigation. Knowledge of the genomic sequence of the SARS-CoV has facilitated the development of rapid diagnostic tests. RNA interference, monoclonal antibody, synthetic peptides, and vaccines are treatment modalities that deserve further investigation. Randomized placebo-controlled studies of the promising treatment modalities are necessary to determine the most appropriate treatment for this highly infectious condition.

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