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REVIEW ARTICLE

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Current concepts in SARS treatment

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Abstract The outbreak of severe acute respiratory syndrome (SARS) has drawn enormous attention and caused fear worldwide since early 2003. The disease appears to be under control now; however, the possible return of SARS must be emphasized. Although many clinical experiments have been reported, the treatment of SARS is largely anecdotal, and so far no treatment consensus has been reached. We summarize 14 clinical reports and attempt to assess the effectiveness of various treatment regimens. A combination treatment of steroids and ribavirin was widely used empirically from the outset of the epidemic. In general, the use of steroids for SARS seemed beneficial, but the optimal timing, dosage, and duration of treatment have not yet been determined. On the other hand, ribavirin administration apparently reduced neither the rate of intratracheal intubation nor that of mortality. Moreover, significant toxicity, such as hemolytic anemia, has been attributed to ribavirin. A few preliminary trials and in vitro data suggest the possibility of treating SARS with interferon. Other agents, including the HIV protease inhibitor glycyrrhizin and convalescent plasma, remain to be evaluated.

Key words SARS · Treatment · Steroids · Ribavirin · Interferons

Introduction

Severe acute respiratory syndrome (SARS) is a newly emerging, readily transmissible, and predominantly pneumonic disease caused by a novel coronavirus referred to as the SARS coronavirus (SARS-CoV).[1–3] It first appeared in Guangdong Province, China, in November 2002[4] and rapidly spread to a total of 29 countries all over the world since late February 2003. This outbreak affected 8098 people and resulted in 774 deaths (mortality rate: 9.6%) by 31 July 2003,[5] drawing enormous attention and causing fear worldwide. The World Health Organization (WHO) declared the end of the worldwide SARS outbreak in July 2003. Although the disease appears to be under control at the time of writing (December 2003), the possible return of SARS should be considered.

Numerous articles on SARS, describing its epidemiology, etiology, diagnosis, clinical features, and management, have been published internationally. Much has been learned about SARS during the several months since the end of the outbreak, but many questions remain unanswered. In particular, the treatment of SARS remains largely anecdotal, and no treatment consensus has yet been reached, since randomized controlled treatment trials were understandably not possible during the outbreak of this novel acute disease. Until we have efficacious vaccines and specific anti-SARS-CoV agents, SARS is likely to remain a major health threat to the world. Here, we review the diverse treatment experiences and controversies to date in order to consolidate our current knowledge and prepare for a possible resurgence of the disease.

Antibiotics

At the first signs of the disease, the administration of broad-spectrum antibiotics such as a fluoroquinolone or β-lactams plus macrolide is warranted because presenting features are nonspecific. Efficient and rapid diagnostic tests are not yet available, especially ones effective in the first few days after onset.[6–8] Upon identification of SARS-CoV, the antibiotic therapy may be withdrawn. In addition to their antibacterial action, macrolides[9] and fluoroquinolones[10] are known to have immunomodulatory properties, but their effect on the course of SARS has not been determined.

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Steroids and ribavirin

On 17 March 2003, WHO called upon 11 laboratories in nine countries to join a network for multicenter research into the etiology of SARS, and on 16 April 2003, WHO announced that a new coronavirus, never before seen in humans or animals, had been identified as the cause of SARS.[11] Steroids and ribavirin were used empirically from the outset of the epidemic in Hong Kong[3,12,13] and Toronto.[14,15] As a result of this experience, So et al.[16] and Lapinsky and Hawryluck[17] proposed a SARS treatment protocol using a combination regimen of steroids and ribavirin.

Corticosteroids are the most commonly used immunomodulatory agents for various critical diseases. They modulate a large number of inflammatory cytokines and play a key role in immune homeostasis.[18] Although the value of corticosteroid therapy for nonviral adult respiratory distress syndrome (ARDS) is controversial,[19,20] some reports have shown the effectiveness of corticosteroids for treating measles pneumonia and viral pneumonias complicating varicella.[21,22]

Ribavirin, a purine nucleoside analogue, hinders the replication of a variety of RNA viruses, although the precise mechanism of action is still to be shown. Ribavirin has been used in combination with interferon a to treat hepatitis C virus infection[23] and as a monotherapy for lassa fever virus infection[24] and severe respiratory syncytial virus (RSV) infection.[25] The effect of ribavirin on murine hepatitis virus, which belongs to the group II coronaviridae, was demonstrated in an animal model.[26,27] In vitro inhibition of RSV, influenza viruses, and parainfluenza viruses is achieved at ribavirin concentrations of 3–10 μg/ml; an oral dose of 600 mg yields peak plasma levels of 1.3 μg/ml, and an intravenous dose of 1000 mg results in a mean plasma concentration of 24 μg/ml.[28]

In Table 1, we summarize 14 clinical reports, outlining the treatment regimen and describing the clinical outcome of SARS patients. Among steroids, intravenous hydrocortisone (HC) 400–800 mg/day (8–12 mg/kg per day) or methylprednisolone (m-PSL) 60–180 mg/day (1–3 mg/kg per day) were first administered, and, if the patient's condition worsened clinically, a pulse dose of m-PSL (0.5–1 g/day) was usually added. Although some studies of cases in which the use of steroids was restricted reported outcomes that were not so poor (Table 1: Nos. 5, 8, 9),[15,29,30] most demonstrated that steroids could lead to early improvements in terms of fever subsidence, less lung infiltration on chest X-ray, and better oxygenation. The rationale for using corticosteroids is based on findings that, paradoxically, clinical deterioration can occur despite a fall in the viral load as IgG seroconversion takes place.[8] Furthermore, lung pathology showed a pronounced increase in alveolar macrophages with hemophagocytosis, which implies immune system hyperactivity due to cytokine dysregulation.[31] In general, the use of steroids for SARS is regarded as beneficial, although the timing, dosage, and duration of treatment are controversial. So et al.[16] proposed that steroid administration should commence if (1) extensive or bilateral chest radiographic involvement is seen; (2) chest radiographic involvement and high fever persist for 2 days; (3) clinical, chest radiographic, or laboratory findings suggest a worsening condition; or (4) oxygen saturation of the room air is <95%. This timing is convincing, whether or not the SARS diagnosis is confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) and other tests, because the disease may be self-limiting in some SARS patients,[30,32] disease severity depend on the patient's age and underlying immune status,[33] and too-early steroid administration may impair the containment of viral replication because of the immunosuppressive effects of the steroids. However, the condition of some patients deteriorates quickly; thus, the course of the disease must be observed carefully. The recommended dosage of steroids varies greatly among hospitals.[16,29,34–36] A study by Ho et al.[36] compared the efficacy between initial use of a low-dose or high-dose steroid regimen (Table 1: No. 11) and suggested that a high-dose (pulsed) m-PSL treatment was more efficacious and equally safe compared with the low-dosage regimens. So et al.[16] reported that a 1 mg/kg per day dose of m-PSL failed to control the fever; they thus increased the initial dose to 3 mg/kg per day and administered pulsed m-PSL only for rescue therapy, if the patient's condition deteriorated further. They also showed that when m-PSL steps 2–3 days long were used during the dose step-down, the symptoms rebounded, so each dose level was continued for 5 days (Table 1: No. 6). Another study that used high-dose steroids, although in combination with interferon a, only upon worsening clinical criteria (Table 1: No. 9) reported a comparably low mortality rate.[29] The steroid dosage should be chosen to counterbalance the degree of hyperimmunity and should be adjusted according to individual age, immunocompetence, and disease severity. It should also be recognized that the prolonged use of high-dose steroids is of concern because further immunosuppression may be detrimental to the patient by encouraging secondary sepsis.[35,37] Recently, there has been some news circulating inside China indicating that quite a few people who contracted SARS have been found to be suffering from avascular necrosis, which is known to occur as a side effect of strong doses of corticosteroids. To determine the optimal timing, dosage, and duration of steroid treatment, randomized controlled trials should be done.

Although the dosage and administration route of ribavirin were quite diverse, ribavirin administration apparently did not reduce the intratracheal intubation or mortality rates (Table 1). Booth et al.[15] used high-dose intravenous ribavirin and reported a mortality rate of 5.6% (Table 1: No. 5); however, they attributed significant toxicity to the ribavirin, including hemolytic anemia and electrolyte disturbances. A comparative trial conducted by Zhao et al.[29] showed that ribavirin, at least when given at a low dose, was basically ineffective (Table 1: No. 9). Furthermore, the use of ribavirin has attracted considerable skepticism because it exhibits no in vitro efficacy against SARS-CoV.[38,39] A post-mortem examination of tissue showed SARS-CoV was not eradicated after ribavirin therapy, and quantitative RT-PCR monitoring of the nasopharyngeal viral load also did not suggest any substantial in vivo antiviral effect from this

Table 1. Treatments and outcomes in patients with SARS

No	Authors (location)	Number of patients (M/F)	Age	Steroid	Ribavirin	Intubation (%)	Deaths (%)	Discharged (%)	Ref.
1	Poutanen et al. (Canada)	10 (6/4)	52.6 (24–79)	Not stated	2 g i.v. followed by 4 g/day i.v. for 4 days, then 2 g/day i.v. for 3 days (7 cases)	5 (50.0)	3 (30.0)	0 (0)	14
2	Tsang et al. (Hong Kong)	10 (5/5)	52.5 ± 11.0 (35–72)	HC 12 mg/kg per day–HC 600 mg/day or m-PSL 240–300 mg/day	24 mg/kg per day i.v. (9 cases), or 3.6 g/day p.o. (1 case)	2 (20.0)	2 (20.0)	1 (10.0)	12
3	Lee et al. (Hong Kong)	138 (66/72)	39.3 ± 16.8	PSL 1 mg/kg per day p.o., when clinically worsened, m-PSL 500 mg/day i.v.	3.6 g/day p.o., when clinically worsened, 1.2 g/day i.v.	19 (13.8)	5 (3.6)	76 (55.1)	13
4	Peiris et al. (Hong Kong)	50 (1.3 : 1)	42 (23–74)	HC 400–600 mg/day i.v. or m-PSL 1–3 mg/kg per day i.v. for 2–3 days, and tailed off over 2–3 weeks (49 cases)	24 mg/kg per day i.v. (49 cases) for 7–10 days	19 (38.0)	1 (2.0)	31 (62.0)	3
5	Booth et al. (Canada)	144 (66/88)	45 (34–57)	HC 20–50 mg/day i.v. (57 cases)	2 g i.v. followed by 4 g/day i.v. for 4 days, then 2 g/day i.v. for 3 days (128 cases)	20 (13.9)	8 (5.6)	103 (71.5)	15
6	So et al. (Hong Kong)	31 (11/20)	39.6 ± 13.3	m-PSL 3 mg/kg per day i.v. for 5 days, 2 mg/kg i.v. for 5 days, PSL 1 mg/kg per day p.o. for 5 days, 0.5 mg/kg per day p.o. for 3 days, 0.25mg/kg per day p.o. for 3 days, when clinically worsened, m-PSL 1 g/day i.v. for 2 days	1.2 g/day i.v. for at least 3 days, then 2.4 g/day p.o.	0 (0)	0 (0)	Not stated	16
7	Peiris et al. (Hong Kong)	75 (36/39)	39.8 ± 12.2	HC 600 mg/day i.v. for 10 days, then PSL 1 mg/kg per day p.o. for 5 days, 0.5 mg/kg per day p.o. for 3 days, 0.25 mg/kg per day p.o. for 3 days, when clinically worsened, m-PSL 0.5 g/day i.v. for 2–3 days	24 mg/kg per day i.v. for 14 days	19 (25.3)	5 (6.7)	27 (36.0)	8
8	Hsu et al. (Singapore)	19 (5/14)	28 (19–73)	HC 400 mg/day i.v. or m-PSL 120 mg/day i.v. for 5 ARDS cases	60 mg/kg per day p.o. for 14 cases	6 (31.6)	3 (15.8)	Not stated	30

Table 1. continued

No	Authors (location)	Number of patients (M/F)	Age	Steroid	Ribavirin	Intubation (%)	Deaths (%)	Discharged (%)	Ref.
9	Z. Zhao et al. (China)	40 30	33.6 ± 13.9 32.4 ± 12.4	Not used restricted use, m-PSL 80–160 mg/day i.v.	400–600 mg/day i.v. Not used	3 (7.5)	2 (5.0) 2 (6.7)	Not stated 2 (6.7)	29
		60	32.5 ± 12.1	when clinically worsened, m-PSL 80–160 mg/day i.v. for 2–3days	Not used	8 (13.3)	7 (11.7)		
		60	30.5 ± 12.3	when clinically worsened, m-PSL 160–1000 mg/day i.v. for 5–14 days	Not used	0 (0)	0 (0)		
10	Chan et al. (Hong Kong)	115 (45/70)	41.0 ± 14.8	HC 600–800 mg/day i.v. or m-PSL 3 mg/kg per day i.v. for 21 days, when clinically worsened, m-PSL 0.5–1 g i.v. for 2 days	1.2 g/day i.v. for 10–14 days.	30 (26.1)	18 (15.7)	82 (71.3)	54
11	Ho et al. (Hong Kong)	55 (23/32)	36 (23–73)	HC 8~12 mg/kg per day i.v. for 3–5 days, PSL 2 mg/kg p.o. or m-PSL 2–3 mg /kg/day i.v. for 5 days, PSL 2 mg/kg p.o. When clinically worsened m-PSL 0.5 g/day i.v. for 3–5 days	24 mg/kg per day i.v. for 7 days, then 3.6 g p.o. for 10–14 days	5 (9.1)	3 (5.5)	Not stated	36
		17 (7/10)	38 (25–82)	m-PSL 0.5 g/day i.v. for 5–7 days or 1 g /day i.v. for 3 days, then PSL 100 mg/day p.o. reducing to 20–30 mg/day on day 21	24 mg/kg per day i.v. for 7 days, then 3.6 g p.o. for 10–14 days	1 (5.9)	1 (5.9)		
12	Wang et al. (China)	96 (20/76)	25.9 ± 10.3	m-PSL 80-160 mg /day i.v. for 3–5 days, 40 mg/day i.v. for 2-3 days, 30 mg/day p.o. for 4–5 days (66 cases)	800 mg/day p.o. for 7–10 days (31 cases)	1 (1.0)	1 (1.0)	95	48
13	Tsui et al. (Hong Kong)	323 (127/196)	41 ± 14 (18–83)	HC 8–12 mg/kg per day i.v. for 14–21days. For 208 cases with progressive pneumonitis, received m-PSL 2.9 ± 2 g/day i.v.	24 mg/kg per day i.v. when clinically worsened, 99 mg/kg /day i.v., followed by 60 mg/kg per day i.v.	42 (13.0)	26 (8.0)	287 (88.9)	53
14	Choi et al. (Hong Kong)	267 (104/163)	39 (18–96)	HC 10 mg/kg per day i.v., when clinically worsened, m-PSL 0.5–1 g/day i.v. for 2–3 days	24 mg/kg per day i.v.	57 (21.3)	32 (12.0)	234 (87.6)	32

Abbreviations used in the table/figure: HC, hydrocortisone; PSL, prednisolone; m-PSL, methylprednisolone; IFN, interferon; ARDS, adult respiratory distress syndrome; SARS, severe acute respiratory syndrome

drug.[8] However, since it has been suggested that ribavirin has some beneficial immunomodulatory effects,[27,40] a well-designed randomized control study is needed to draw firm conclusions.[41]

Interferons

Interferons, a family of cytokines important in the cellular immune response, have been shown to be partly effective against animal and human coronaviruses.[42–44]

An in vitro examination of interferons against SARS-CoV was recently carried out using interferon α-2b, interferon β-1b, and interferon γ-1b.[45] Interferon b was found to be more potent than interferon α or γ, and it remained effective after viral infection, although the potential difference between interferon a and b has been debated.[46,47] The use of interferons in the treatment of SARS has been limited to interferon a in combination with steroids, immunoglobulins, or thymic peptides, and its efficacy cannot be ascertained.[29,48] In preliminary data from Canada,[49] a faster recovery was observed anecdotally in a small Canadian series in which consensus interferon a (alfacon-1), which shares 88% homology with interferon α-2b and about 30% homology with interferon β, was used. These results suggest that interferons are promising and should be tested in future SARS treatment trials.

Alternative agents

A lopinavir–ritonavir coformulation (Kaletra) is a protease inhibitor preparation used to treat human immunodeficiency virus (HIV) infection. It was used in combination with ribavirin in some Hong Kong hospitals in the hope that it would inhibit coronaviral proteases, thus blocking the processing of the viral replicase polyprotein and preventing the replication of viral RNA. Preliminary results suggest that the use of lopinavir–ritonavir simultaneously with ribavirin and corticosteroids might reduce intubation and mortality rates, especially when administered early.[50] It thus appears worthwhile to conduct controlled studies on this promising class of drugs.

Glycyrrhizin, which is used in the treatment of chronic hepatitis and is relatively nontoxic, has been tested in vitro and found to be an active agent against SARS-CoV.[39] It inhibited viral adsorption and penetration, and was most effective when administered both during and after the viral adsorption period. It was postulated that its mechanism of action is mediated by the nitrous oxide pathway.

Gamma immunoglobulins were used in some hospitals in China and Hong Kong.[29] However, because other therapies such as corticosteroids were often used concomitantly, their effectiveness against SARS remains uncertain. Convalescent plasma, collected from recovered patients, also remains to be evaluated.

Assisted ventilation

As shown in Table 1, about 10%–20% of SARS patients eventually required intubation and mechanical ventilation owing to severe respiratory failure.

Noninvasive positive pressure ventilation (NIPPV) was commonly employed in many Chinese hospitals,[29] and was found to avert the need for intubation and invasive ventilation in up to two-thirds of SARS patients with deterioration.[51] NIPPV can be given using a continuous positive airway pressure of 4–10 cm H_2O or bilevel pressure support with an inspiratory positive airway pressure of < 10 cm H_2O and an expiratory positive airway pressure of 4–6 cm H_2O. Although NIPPV is useful, the infective risks associated with aerosol generation have hampered its use in many hospitals.[35] Highly rigorous infection control measures, in addition to the standard infection control measures recommended for aerosol-generating procedures, should be utilized.

The ventilatory management of patients with SARS does not differ from that of patients with ARDS.[17] Both pressure and volume control ventilation can be employed. The tidal volume should be kept low at 5–6 ml/kg of body weight, and plateau pressures should be kept at < 30 cm H_2O. Positive end-expiratory pressure should also be titrated to as low a value as possible to maintain oxygenation, because pneumothorax and pneumomediastinum are known complications of SARS even without assisted positive pressure ventilation,[8] and a high rate (34%) of barotrauma has been reported.[52]

Concluding remarks

We have not experienced a SARS outbreak in Japan and therefore have no domestic information about SARS treatment. Thus, we recently visited Tan Tock Seng Hospital in Singapore and Sunnybrook and Women's College Health Centre in Toronto, Canada, where many SARS patients were treated. We asked the physicians in charge for their impressions of the effectiveness of various SARS treatments and got some responses, as follows. They did not find ribavirin to have any clinical benefit and do not intend to use it in the future; steroids should be used cautiously, taking into account disease severity, because in some patients the disease is self-limiting. Thus, it is difficult to recommend any established treatment protocol at this time.

Pending the development of vaccines and new drugs specific for SARS and the results of well-conducted randomized controlled studies on a sufficient number of cases, we have to rely on the existing treatment modalities described and discussed in this review.

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