Treatment of Severe Acute Respiratory Syndrome

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CHAPTER 9

Background

Severe acute respiratory syndrome (SARS) is a newly emerged disease and the epidemic in Hong Kong came as a crisis. The clinical course of SARS appears to follow a triphasic pattern [1,2]: phase I is clinically characterized by fever, myalgia and other systemic symptoms that generally improve after a few days. This is the phase when active viral replication occurs. Phase II is characterized by recurrence of fever, oxygen desaturation and radiological progression of pneumonia. The clinical progression during phase II appears to be related to immuno-pathological damage. The majority of patients recovered spontaneously but in some the disease progressed into phase III, characterized by acute respiratory distress syndrome (ARDS) necessitating ventilatory support (Figure 9.1). Reports show that with the development of respiratory failure and ARDS, 15–30% of patients will require intensive care admission [3].

Histological examination shows the presence of coronavirus particles in the alveoli of the infected lungs. Histopathology of post-mortem cases also reveal diffuse alveolar damage, pulmonary oedema, hyaline membrane formation and highly activated macrophages with haemophagocytosis. Thus, the treatment modalities should include antivirals, immuno-modulators and respiratory support at the different stages of the diseases [3,4].

Key points

Triphasic clinical pattern

1. *Viral replication*: fever, myalgia and other systemic symptoms that generally improve after a few days.
2. *Immuno-pathological damage*: recurrence of fever, oxygen desaturation and radiological progression of pneumonia.
3. *Recovery* (most patients) or *progression to ARDS*.

General approach

The treatment protocol used in Hong Kong included the use of broad-spectrum antibiotics. Initial treatment usually consists of intravenous (IV) cefelosporin in combination with macrolides or quinolones.

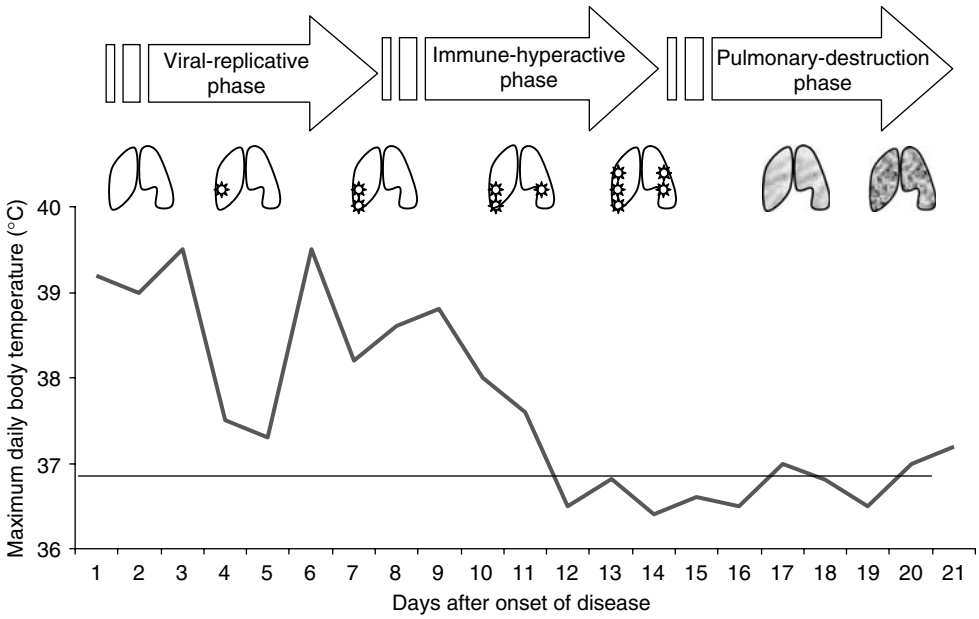

Fig. 9.1 A triphasic presentation of SARS.

A combination of ribavirin with or without 'low-dose' corticosteroid therapy is commenced when patients fail to respond to antibiotics treatment for 2 days. Pulses of high-dose methylprednisolone are given as a response to persistence or recurrence of fever and radiographic progression of lung opacity ± hypoxaemia despite initial combination therapy. Further pulses of methylprednisolone can be given, if there is no clinical or radiological improvement.

Patients who develop hypoxaemia are given supplemental oxygen therapy. Patients would be admitted to the intensive care unit (ICU) when severe respiratory failure develops as evidenced by:

1. failure to maintain an arterial oxygen saturation of at least 90%, while receiving supplemental oxygen of 50% and/or
2. respiratory rate greater than 35 breaths per minute.

Non-invasive positive-pressure ventilation is used by some centres but avoided in the others because of the fear of viral transmission potentially resulting from mask leakage and flow compensation. Criteria for intubation and positive-pressure ventilation are, in general:

1. persistent failure to achieve arterial oxygen saturation of 90% while receiving 100% oxygen via a non-rebreathing mask and/or
2. onset of respiratory muscle fatigue as evidenced by an increase in the partial pressure of carbon dioxide ($PaCO_2$), sweating, tachycardia and/or a subjective feeling of exhaustion.

Mechanical ventilation with synchronized intermittent mandatory ventilation (SIMV) or pressure control ventilation are often instituted.

Figure 9.2 summarizes the treatment protocol adopted at the Prince of Wales Hospital in Hong Kong.

Key points

Treatment protocol

1. Broad-spectrum antibiotics.
2. If no response, then change to ribavirin with/without corticosteroids.
3. If there is persistence or recurrence of fever and radiographic progression of lung opacity ± hypoxaemia, then give pulses of high-dose methylprednisolone.
4. If hypoxaemic, then give supplemental oxygen therapy.

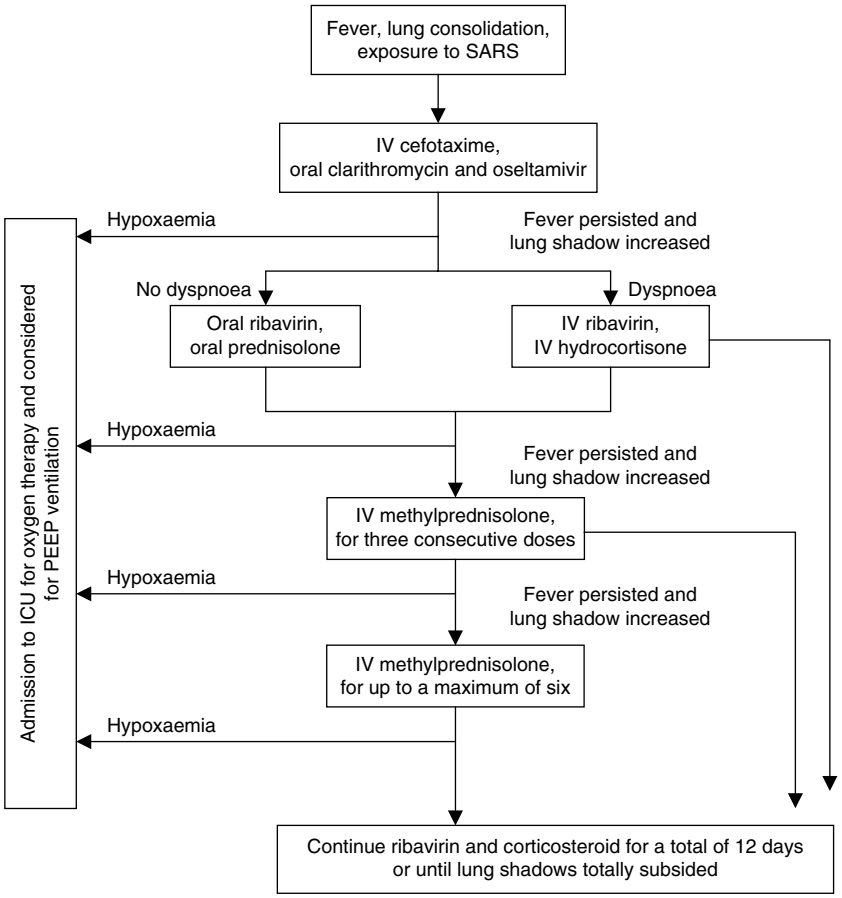

Fig. 9.2 Treatment protocol for SARS.

Key points

ICU admission

1. Failure to maintain an arterial oxygen saturation of at least 90% while receiving supplemental oxygen of 50% and/or
2. Respiratory rate greater than 35 breaths per minute.

Key points

Intubation criteria

1. Persistent failure to achieve arterial oxygen saturation of 90% while receiving 100% oxygen via a non-rebreathing mask and/or
2. Onset of respiratory muscle fatigue as evidenced by an increase in $PaCO_2$, sweating, tachycardia and/or a subjective feeling of exhaustion.

Clinical outcome

The clinical response to treatment can be objectively assessed by changes in body temperature, resolution of radiological lesions and oxygen requirement to maintain arterial oxygen saturation. At the Prince of Wales Hospital, sustained response to therapy is defined as:

1. defervescence (daily peak temperature $\leqslant 37.5°C$) for at least 4 consecutive days,

2. radiological improvement, as assessed by three radiologists blinded to the clinical data, of more than 25% and
3. oxygen independence as assessed by pulse oximetry (oxygen saturation ⩾95% on room air) on the 4th afebrile day.

Patients with defervescence who achieved either resolution of lung consolidation or oxygen independence, but not both, are classified as showing a partial response. Patients who fall short of criteria 2 and 3 above are classified as non-responders to therapy.

Key points

Clinical response

1. ⩽37.5°C for at least 4 consecutive days
2. Radiological improvement
3. Oxygen saturation ⩾95% on room air on the 4th afebrile day.

Antiviral agents

Genomic analysis identified two types of targets for antiviral therapy. The surface targets for cell entry and the enzymatic targets for viral replication, i.e. the RNA replicase and the protease (Figure 9.3).

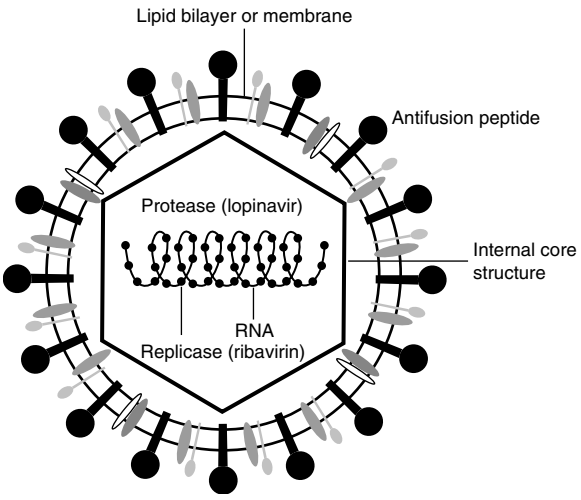

Fig. 9.3 Possible targets for coronavirus are surface target for cell entry and enzymatic targets for cell replication.

Ribavirin is an inhibitor of replicase. The choice of ribavirin in the treatment of SARS was based on the following reasons:

- Before the sensitivity of SARS-associated coronavirus (SARS-CoV) was known, ribavirin was chosen because of its broad-spectrum antiviral activity for both RNA and DNA viruses (respiratory syncytial virus, influenza A and B, measles and parainfluenza as well as Lassa fever).
- *In vitro* study using plague reduction assay showed that ribavirin has a modest activity against SARS-CoV at the concentration of 50 μg/mL [5]. Unfortunately, more recent study revealed that ribavirin has no significant *in vitro* activity against this novel coronavirus, believed to be responsible for SARS [6].
- Besides a mild antiviral activity, ribavirin has been shown, in a coronavirus hepatitis murine model, to have a modest immuno-modulatory effect. Ribavirin has been shown to inhibit viral-induced macrophage production of pro-inflammatory cytokines and T-helper 2 cells (Th2) cytokines. As immunological reaction is believed to play a part in the pathogenesis of pulmonary injury, ribavirin may have some beneficial effect also in this aspect.

In fact, reviewing our data on ribavirin and low-dose steroid combination, the treatment has not produced any significant benefit in the treatment of SARS.

Based on the results of our cohort of 138 patients, favourable response to ribavirin was found in a minority of patients. Ninety-four patients received oral ribavirin and prednisolone. Among them, there were 14 sustained responders and nine partial responders. These 23 patients were discharged uneventfully. Two patients died in the early phase of the disease before additional therapy could be given. Forty-four patients received IV ribavirin and hydrocortisone and, among them, only two had a sustained response whereas four patients died (Figure 9.4). This combination therapy failed to show any appreciable response in the remaining 107 patients (Table 9.1). With the current dose of ribavirin used, we observed the modest degree of anaemia in most patients (59% dropping haemoglobin (Hb) by 2 g/dL), probably the result of haemolysis. A much higher dose of ribavirin, based on the dosage for treatment of haemorrhagic fever

viruses, has been reported to be associated with more significant toxicity. In a report from the Toronto group [7], haemolysis was reported in 76% and a decrease in Hb of 2 g/dL in 49%, elevated transaminases in 40% and bradycardia in 14% of SARS patients.

Based on these results, ribavirin cannot be recommended as a first-line therapy for coronavirus infection.

The other antiviral therapy that has been put to test is lopinavir. Lopinavir is a protease inhibitor used in the

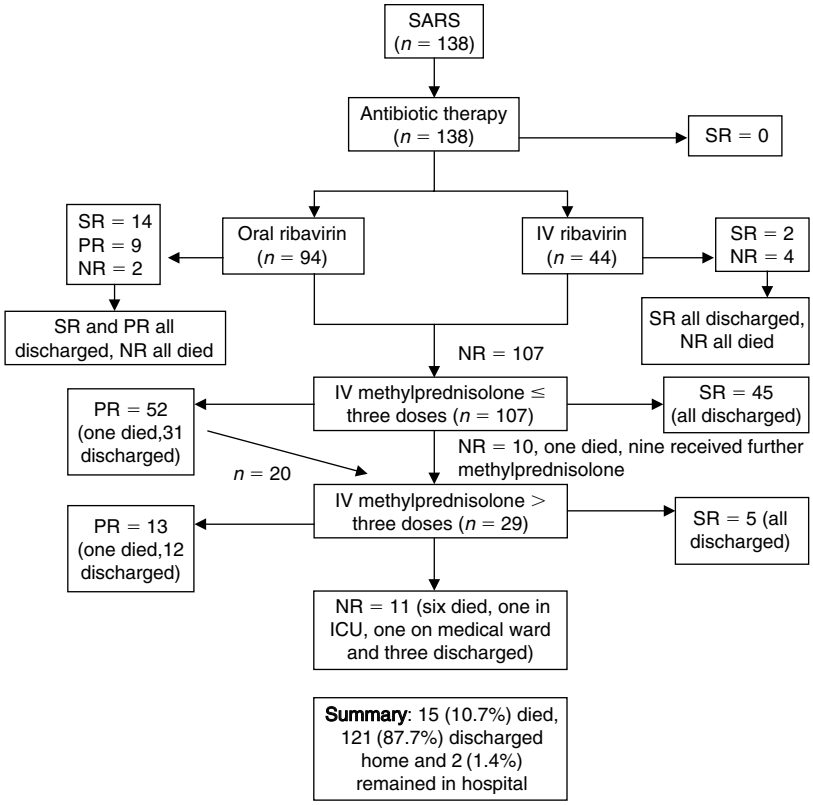

Fig. 9.4 Clinical outcome of 138 patients with SARS. SR: sustained response; PR: partial response; NR: no response.

Table 9.1 Clinical response to therapy.

	Broad-spectrum antimicrobial[a] (%), *n* = 138	Ribavirin + corticosteroid[b] (%), *n* = 138	IV methylprednisolone[c] (%), *n* = 107
SR	0 (0)	16 (11.6)	50 (46.7)
PR	0 (0)	9 (6.5)	45 (42.1)
NR	138 (100)	113 (81.9)	12 (11.2)

[a]Antimicrobials included cefotaxime and clarithromycin (or levofloxacin) plus oseltamivir.
[b]Ribavirin (oral or IV) plus oral prednisolone or IV hydrocortisone.
[c]IV methylprednisolone up to 3 g in total.
Clinical outcome definitions: (1) afebrile (daily peak temperature ⩽37.5°C) for at least 4 consecutive days; (2) resolution of chest radiograph consolidation by >25% (comparing film of maximal consolidation and that on the 4th afebrile day) and (3) oxygen independence (oxygen saturation ⩾95% on room air) on the 4th afebrile day.
Sustained response (SR): 1 + 2 + 3; partial response (PR): 1 + 2 or 3 and no response (NR): fail to fulfil the criteria of SR and PR.

treatment of human immunodeficiency virus (HIV). Lopinavir is combined with ritonavir (as Kaletra™) to reduce its metabolism in the body. *In vitro* data suggest that lopinavir has a much-augmented activity against SARS-CoV. The 50% inhibitory activity of lopinavir is around 4 μg/mL, around 10-fold higher than that of ribavirin [5]. In a pilot study of using Kaletra™ as initial treatment of SARS and compared to historic control of ribavirin-treated (age- and sex-matched) patients, the oxygen desaturation rate, requirement of intubation and mechanical ventilation as well as mortality of the former was significantly reduced. These results, however, are retrospective and uncontrolled. Interpretation must be taken with caution.

Key points

Ribavirin

- Inhibitor of replicase
- Antiviral activity for both RNA and DNA viruses
- ? *in vitro* activity against SARS-CoV
- Modest immuno-modulatory effects in coronavirus hepatitis murine model
- Cohort of 138 patients showed favourable response in the minority of patients

Ribavirin side effects

- Haemolysis (76%)
- Decrease in Hb of 2 g/dL (49%)
- Elevated transaminases (40%)
- Bradycardia (14%)

Ribavirin cannot be recommended as a first-line therapy for coronavirus infection.

Immuno-modulators

Previous studies have shown that in acute viral respiratory infections, large amounts of early-response cytokines, such as interferon alpha (IFNα), tumor necrosis factor alpha (TNFα), interleukin (IL)-1 and IL-6 are produced. These cytokines mediate antiviral activities but at the same time may contribute to tissue injury. The finding of activated macrophage in the lung, haemophagocytosis and overproduction of cytokines in patients with SARS have prompted the idea of using immuno-modulators to suppress over-reaction of the body immune system. The most commonly used immuno-modulators are corticosteroids.

In our cohort of 138 cases at the Prince of Wales Hospital, IV pulse therapy with high-dose methylprednisolone was given to 107 patients who did not respond to ribavirin and 'low-dose' corticosteroid therapy. After three infusions of 0.5 g methylprednisolone, 45 patients (42.1%) showed a sustained response and recovered from the disease. Fifty-two patients (48.6%) demonstrated a partial response to the therapy. Among those with a partial response, 31 recovered and were discharged from hospital, one died, whereas 20 required further pulses of high-dose methylprednisolone. There were 10 non-responders, and among them one died. Among the partial responders and non-responders, 29 received further doses of IV methylprednisolone for up to 3 g in total. Sustained response was reported in five and partial response in 13. Eleven patients (median age 55 years, range 33–82 years) failed to show any response to more than three pulses of high-dose methylprednisolone. Among them, six patients died, one remained in the ICU, one remained on medical ward, while three were discharged home (Figure 9.4). The overall success rate of high-dose methylprednisolone therapy was 88.8% (Table 9.1).

The side effects of high-dose corticosteroids are well known. In this cohort, hyperglycaemia (plasma spot glucose ⩾11.0 mmol/L) was detected in 21.5% of patients and hypokalaemia in 15%. These metabolic derangements were easily corrected when IV high-dose methylprednisolone was discontinued. Two patients developed transient confusion, delusion and anxiety which subsided after discontinuation of steroid. The risk of nosocomial infection is reckoned with the use of high-dose steroid. In our series, however, secondary bacterial or fungal infection was reported in 11 (10.2%) of patients.

Following high-dose methylprednisolone therapy, rapid resolution of lung opacity is usually followed by improvement of hypoxaemia. Most patients responded after receiving three doses of high-dose methylprednisolone (up to 1.5 g in total). Less than 30% of cases required additional doses. The timing of administration of high-dose methylprednisolone is important.

It should be administered only during phase II when radiological progression of consolidation and increasing hypoxaemia were documented. In most cases, high-dose methylprednisolone was given at the end of the 1st week. We have avoided high-dose methylprednisolone in the early phase of SARS, as viral clearance by host immunity might be hampered. It must be emphasized that high-dose methylprednisolone should not be used only to control fever. In some of our patients, the lung opacities continued to deteriorate even after defervescence. In these patients, the benefit of high-dose methylprednisolone in reversing radiological progression is also seen. While we recognize that the benefit of high-dose methylprednisolone cannot be confirmed without a control group, the use of high-dose corticosteroid in the treatment of SARS warrants further investigation.

Other immuno-modulating agents that have been used included IV immunoglobulin (IVIG), pentaglobulin, azathioprine and anti-TNF in small number of patients. The numbers of cases were small and as experience was anecdotal, it is difficult to confirm the efficacy of these treatments. *In vitro* tests have also indicated that IFN has antiviral activity against SARS-CoV. IFN has been used in the treatment of viral infections. However, to date, there is no clinical data on its use in the treatment of SARS. There are concerns that IFN might aggravate the injurious effects of cytokines.

Key points

IV pulse therapy with high-dose methylprednisolone

- Given to patients who did not respond to ribavirin and 'low-dose' corticosteroid therapy
- Overall success rate of 88.8%
- Administered only during phase II, when there is radiological progression and increasing hypoxaemia

Side effects of high-dose methylprednisolone

- Hyperglycaemia (21.5%)
- Hypokalaemia (15%)
- Transient confusion, delusion and anxiety

Convalescent plasma

The Prince of Wales Hospital was the first to use convalescent plasma for the treatment of SARS. Convalescent plasma was obtained from patients who recovered from the illness.

These patients

- were afebrile for at least 7 consecutive days,
- had radiographic improvement by at least 25%,
- no further need of oxygen supplement,
- passed 14 days since onset of symptoms.

All donors had to screen negative for hepatitis B, C, HIV and veneral disease research laboratory slide test (VDRL), and had to be confirmed to be seropositive for SARS-CoV.

Apharesis was performed using a cell separator. Blood volume that was processed ranged from 2000 to 2500 mL. An average of 600–900 mL of serum was harvested per patient. Normal saline was used for replacement of fluid volume. Calcium gluconate (10% solution, 10 mL/1000 mL serum extracted) was given to the donor as replacement.

At the Prince of Wales Hospital cohort, 40 patients had progressive disease after three doses (500 mg each) of pulsed methylprednisolone. Nineteen patients received convalescent plasma after the three doses of pulsed methylprednisolone, two of whom received further pulsed methylprednisolone after plasma infusion. They were compared to 21 patients who received only pulsed methylprednisolone. Seventy-four per cent of the patients who received convalescent plasma were discharged by day 22 as compared with 19% in the group that received steroid alone ($P = 0.001$). There were no differences between age, sex and admission lactate dehydrogenase (LDH) between the convalescent plasma group and steroid group (Table 9.2). There were five deaths in this cohort study, all occurring in patients receiving steroids only, as compared with no death in the serum group ($P = 0.049$). Hospital stay was significantly longer in those who received steroid alone. Our preliminary results with convalescent plasma indicate that it might be beneficial in 'neutralizing' the virus in the infected host. Yet, to achieve the maximum benefit, convalescent plasma should be given early. This promising result of convalescent plasma also prompts the development of hyperimmune globulin (monoclonal antibody) as a therapeutic agent in the future.

Table 9.2 Comparison of treatment outcome between those who received convalescent plasma (after failed response to corticosteroid) and those who received corticosteroid alone.

	Convalescent plasma	Corticosteroid	*P*
Number of patients	19	21	
Age	38.7	47.9	0.087
LDH (IU/L) on admission	256.1	247.7	0.7
Patients discharge by day 22	73.4% ($n = 14$)	19% ($n = 4$)	0.001
Patients discharged by day 22 after adjustment of co-morbidities	77.8% (14/18)	23% (3/13)	0.004
Mortality rate	0%	23.8% ($n = 5$)	0.049

Key points

Convalescent plasma

- Should be given early in course of disease
- Results in earlier hospital discharge
- Less deaths

Ventilatory support

Patients who developed hypoxaemia were given supplemental oxygen therapy. Oxygen was delivered by nasal catheters or in combination with oxygen mask. A surgical mask was applied, if the patient was using nasal catheter alone. Use of high-flow Venturi-type masks should be avoided to avoid dissemination of droplets if patient cough. Nebulization should be avoided for the same reason.

Patients were admitted to the ICU when severe respiratory failure developed as evidenced by:

1. failure to maintain an arterial oxygen saturation of at least 90% while receiving supplemental oxygen of 50% and/or
2. respiratory rate greater than 35 breaths per minute.

Criteria for intubation and positive-pressure ventilation were:

1. persistent failure to achieve arterial oxygen saturation of 90% while receiving 100% oxygen via a non-rebreathing mask and/or
2. onset of respiratory muscle fatigue as evidenced by an increase in $PaCO_2$, sweating, tachycardia and/or a subjective feeling of exhaustion.

Mechanical ventilation with SIMV, or pressure control ventilation, was instituted. Positive end-expiratory pressure (PEEP) and inspired oxygen concentration was titrated to achieve an arterial saturation of 90–95%. Tidal volume should be maintained at 6–8 mL/kg estimated body weight and plateau pressure maintained at 30 cmH_2O or less. $PaCO_2$ is allowed to rise provided the pH was greater than 7.15. Patients unable to meet the above parameters can be ventilated in the prone position.

Non-invasive positive-pressure ventilation was avoided because of the risk of viral transmission potentially resulting from mask leakage and flow compensation, possibly causing wide dispersion of contaminated aerosol. Yet, experience from China has alluded that if low pressure ventilation was used in a room with good ventilation, dissemination of droplet and cross-infection would not be a major problem.

Key points

Supplemental oxygen

- Nasal catheters or in combination with oxygen mask
- Surgical mask applied, if using nasal catheter alone
- High-flow Venturi-type masks or nebulization should be avoided

New treatment

Recently, there has been interest in the use of herbal medicine against SARS. Glycyrrhizin, an active component of liquorice roots, for instance, has been

recently shown to be active *in vitro* against 2SARS-CoV [8].

Other agents that have been tried in SARS patients include immuno-modulators such as IVIG and pentaglobin (IgM-enriched IGs). It has been postulated that these compounds may act via different mechanisms in the modulation of the systemic sepsis response, including neutralizing endotoxins and exotoxins, and scavenging active complement components and lipopolysaccharides.

These compounds have been used in SARS patients who have failed conventional therapy (e.g. IVIG 0.4 g/kg for 5 days, or pentaglobin 300 mL IV over 12 hours for 3 days). Their efficacy and safety, as well as other novel treatment strategies in SARS patients, remain to be determined; and no formal recommendations could be given for their use at this stage.

Key points

New treatment

- Antiviral and immuno-modulatory agents
- Lack of evidence excludes recommendation at this stage

Conclusion

At present, the most efficacious treatment regime for SARS is still not known. There is no formal treatment recommended except for meticulous supportive care.

The use of specific antiviral and immuno-modulatory therapies directed against the SARS-CoV such as ribavirin and corticosteroids, remain experimental and controversial at this stage.

Randomized controlled studies will be required to evaluate the efficacy and best timing for high-dose methylprednisolone therapy.

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