Commentary

# Pharmacologic Treatment of SARS: Current Knowledge and Recommendations

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## Abstract

**The severe acute respiratory syndrome (SARS) pandemic caught the world by surprise in 2003 and spread rapidly within a relatively short period of time. Hence, randomised placebo-controlled clinical trials on the treatment of SARS were not possible. Our understanding was obtained from observational, cohort studies, case series and reports. Nevertheless, such information is useful in providing clinical management guidelines and directing future research in case SARS recurs. Early in the pandemic, a combination of ribavirin and corticosteroids was adopted as the standard treatment in Hong Kong, Canada and elsewhere because of the apparent good results of the first few patients. Subsequent reports showed that ribavirin was associated with a high rate of toxicity and lacked in vitro antiviral effect on SARS-coronavirus (SAR-CoV). The timing and dosage regimens of steroid in the treatment of SARS are controversial. Pulse methylprednisolone 250 to 500 mg/day for 3 to 6 days has been reported to have some efficacy in a subset of patients with "critical SARS," i.e., critically ill SARS patients with deteriorating radiographic consolidation, increasing oxygen requirement with $PaO_2$ <10 kPa or $SpO_2$ <90% on air, and respiratory distress (rate of 30/min). Prolonged therapy with high-dose steroids, in the absence of an effective antimicrobial agent, could predispose patients to complications such as disseminated fungal infection, and avascular necrosis. Kaletra (400 mg ritonavir and 100 mg lopinavir), a protease inhibitor used in the treatment of human immunodeficiency virus infection, may be considered for early treatment of SARS patients, preferably in a randomised double-blind placebo-controlled clinical trial setting. Interferon (IFN) is not recommended as standard therapy in SARS. However, there are enough data on in vitro activity of IFN preparations and a few clinical studies for these products to support a controlled trial if SARS recurs. Many other experimental treatments have been tried in an uncontrolled manner, and they should not be recommended as standard therapy.**


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## Introduction

Acute respiratory failure, which occurred in 20% to 25% of severe acute respiratory syndrome (SARS) patients and necessitated ICU admission, was the primary cause of morbidity and mortality during the 2003 pandemic.[1-5] Even with aggressive treatment in the ICU, about half of those who required mechanical ventilation died.[5-7] SARS has been succinctly described as "acute respiratory distress syndrome (ARDS) plus intensified respiratory isolation."[8] The overall global case fatality of SARS during the 2003 pandemic was 9.6% (774/8096).[9]

## Rationale for Treatment

SARS manifests within a spectrum of severity, with a highly individualised rate of progression through the different phases of viral replication, inflammatory pneumonitis and residual pulmonary fibrosis.[10] Autopsy studies have shown haemophagocytosis in lungs, which may be due to cytokine storm or dysregulation triggered by the SARS-coronavirus (SARS-CoV).[1,11]

In the absence of an effective specific antiviral therapy, the treatment of SARS remained supportive and 90% of patients survived. However, in severely ill or deteriorating patients, antiviral agents to prevent viral replication, plus antibacterial agents as indicated, as well as anti-inflammatory therapy to prevent inflammatory pneumonitis and irreversible pulmonary fibrosis appear reasonable.[12] Antiviral agents used in the empiric therapy of SARS

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include ribavirin, interferon (IFN)-α and lopinavir-ritonavir.[4]

## Ribavirin

Ribavirin is a nucleoside analogue with in vitro activity against a number of RNA and DNA viruses, including human metapneumovirus and some animal coronaviruses.[13,14] It also has immunomodulatory activity and was used empirically in the early stages of the epidemic in an attempt to reduce viral load and prevent respiratory complications.[15] Hence, many patients early in the epidemic were treated with ribavirin and corticosteroids.[1,16] The first few patients showed very good progress and recovery, probably due to their young age and good premorbid health.[17] Hence, this combination was used as a standard anti-SARS regime routinely in Hong Kong, Canada and other countries.[1,3,16,18-20]

Various regimens of oral and intravenous (IV) ribavirin were used widely. The usual regimen was IV 8 mg/kg tid for the first 5 days, followed by oral 1200 mg tid for a total of 10 to 14 days.[16,21] Initial studies reported improvements in surrogate markers of outcome, such as resolution of fever, and improvement in oxygenation and radiographic appearance.[1,16,20] However, these observational case series were not controlled and most patients also received corticosteroids.

Ribavirin therapy was associated with many adverse effects (Table 1),[2,10,22-26] including haemolytic anaemia in 33% to 73%,[2,24-26] hypocalcaemia in 58%,[24] and hypomagnesaemia in 46% of patients.[24]

In vitro testing using cell culture-based assays showed that ribavirin has no selective antiviral activity against SARS-CoV.[27] There was also no evidence of its clinical efficacy in a number of clinical studies.[2,24,28] SARS patients who received ribavirin and had fatal outcome still had polymerase chain reaction and electron microscopic evidence of SARS-CoV in the lung.[11,29]

In patients treated with combinations of ribavirin and corticosteroids, there was a marked increase in viral load in their upper respiratory tract during therapy.[30] Such clinical findings are consistent with ribavirin's lack of in vitro antiviral effects and the confounding effect of systemic corticosteroids on viral replication.[14] Routine use of ribavirin is currently not recommended.[31,32]

## Corticosteroids

The respiratory disease typically progressed during the second week of illness when virus loads were decreasing and antibody titres were increasing.[30] Lung damage in SARS patients may be immune-mediated and pathological findings were consistent with cytokine dysregulation.[33] The judicial use of corticosteroid therapy for deteriorating SARS patients has been shown to be associated with significant and sometimes dramatic radiological and clinical improvement (decrease in fever and the need for oxygen supplementation) without any effect on mortality.[11,18,34] Computed tomography (CT) of thorax have demonstrated features of bronchiolitis obliterans organising pneumonia (BOOP), which is steroid-responsive.[1,2,25,35] However, many patients worsened clinically despite receiving corticosteroid treatment, and higher doses or pulse steroid were required as rescue therapy.[18,25] Three steroid regimens were commonly used (Table 2).[10,16,18,21,25,36,37]

Three groups of responders (in terms of clinical and radiological improvements), even with the same steroid treatment regimen, could be identified.[21] Among the "good" responders, a proportion developed a worsening of the disease with fever, respiratory failure and more extensive radiographic disease than at presentation. This often occurred during week 2 to 3 of their illness when the dosage of methylprednisolone (MP) was tapered. Most of these "rebound" patients responded to a second pulse MP therapy. The second group of patients included "fair" responders who responded to a higher dose and more prolonged administration of MP. Less than 10% were "poor" responders who did not improve or even significantly deteriorated despite prolonged pulse MP, ribavirin and antibiotic therapy. Poor responders were frequently older

Table 1. Adverse Effects of Ribavirin

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| Haemolytic anaemia, leukopaenia, thrombocytopaenia |
| Reticulocytosis |
| Hypocalcaemia, hypomagnesaemia, hypokalaemia, hyperuricaemia |
| Bradycardia |
| Nausea, vomiting, diarrhoea |
| Chest pain, dyspnoea, rhinitis, pharyngitis |
| Sleep disturbance, irritability, arthhralgia, paraesthesia, blurring of vision |
| Influenza-like illness, dizziness, arthralgia, headache |
| Thyroid disease |
| Rash, pruritis, alopecia, dry skin |
| Taste disturbance |
| Teratogenicity |

Table 2. Common Steroid Regimens in SARS

1. IV hydrocortisone 2 mg/kg qid or 4 mg/kg tid, followed by oral prednisolone for varying periods and doses as per clinical evaluation.
2. IV methylprednisolone 1-2 mg/kg qid or 2 to 4 mg/kg tid, followed by oral prednisolone for varying periods and doses as per clinical evaluation.
3. IV pulse methylprednisolone 500 mg daily x 5 days, followed by maintenance oral prednisolone 50 mg bid reducing to 20 to 30 mg daily on day 21 as per clinical evaluation.

patients (>50 years) with comorbidities.

A retrospective study of 72 probable SARS patients showed that those who received pulse steroid (n = 17; MP ≥500 mg/day) as initial steroid therapy had less oxygen requirement, better radiographic outcome, and less likelihood of requiring rescue pulse steroid therapy than their counterparts on a lower initial dosage (n = 55; MP <500 mg/day).[25] There was no difference between the 2 groups in cumulative steroid dosage, ICU admission, mechanical ventilation, risk of death, haematological and biochemical parameters and side effects (haemolytic anaemia, secondary infections or haemetemesis), except that patients in the pulse steroid group had less hyperglycaemia.

A prospective, uncontrolled study (n = 138) using a stepwise treatment protocol in those patients who failed to improve after a combination of ribavirin and low-dose corticosteroids showed that IV high-dose pulse MP (n = 107) was efficacious in improving clinical and radiographic parameters.[10] At 4 months after the outbreak of this study cohort, 15 (10.9%) died, 122 (88.4%) were discharged home and 1 (0.7%) remained in hospital.

A retrospective study of 53 patients from Guangzhou found that a lower dose of steroids (IV MP 2 to 3 mg/kg/day for 4 days) could result in 30% improvement in chest X-rays and/or 20% increase in oxygenation in 53% of patients.[38]

In one multivariate analysis of 218 patients with SARS, the use of pulse corticosteroid therapy was strongly associated with mortality, although the results are difficult to interpret because the sickest patients typically received pulsed corticosteroids as salvage therapy.[39]

Another retrospective cohort study of 78 patients showed that patients treated with corticosteroid had a 20.7-fold increased risk of either ICU admission or mortality, independent of their age and disease severity as represented by peak lactate dehydrogenase level.[40]

In patients who died 50 days into their illness, postmortem studies detected high viral loads, which suggested that persistent viral replication contributed to the lung damage.[29] Corticosteroids could potentially increase or prolong viral replication and worsen disease. Prolonged and high-dose corticosteroid therapy is associated with a number of complications including immunosuppression and opportunistic infections, particularly ventilator-associated pneumonia and even invasive fungal infections,[4,36,41-43] and avascular necrosis (AVN).[44]

In Hong Kong, around 12% (49 out of 418) of patients with SARS were found to have magnetic resonance imaging-proven AVN of the hips and knees.[17] The dosage and duration of steroid usage is common for patients suffering from organ transplant rejection, who do not have such a high incidence of AVN.[43] The pathogenesis of AVN and other extrapulmonary manifestations in SARS, including residual diastolic cardiac dysfunction and liver dysfunction,[45,46] is unclear.

The current recommendation is to consider moderate to high-dose steroids (MP 250 to 500 mg/day for 3 to 6 days) for severely ill patients presenting with deteriorating radiographic consolidation, increasing oxygen requirement with $PaO_2$ <10 kPa or $SpO_2$ <90% on air,[31,32] and respiratory distress (rate of 30/min), i.e., the syndromes of "critical SARS".[37] Steroids should not be used in the early phase of SARS, but rather as rescue therapy, as it may impair host viral clearance.[10]

**Interferons**

Interferons (IFNs) are potent broad spectrum antiviral agents and IFN-a has been used in the treatment of hepatitis B and C.[4]

A 4-arm trial from Guangzhou examined ribavirin IV 0.4 to 0.6 g/day (Group A) and IFN-α IM 3 million units per day (Groups B, C and D), with different doses of corticosteroids.[47] The ribavirin arm (Group A) and one of the IFN-α arms (Group B) received no steroids during the first 14 days of treatment. Group C received MP 80 to 160 mg/day for 2 to 3 days when symptoms worsened or pulmonary infiltrates increased. Group D received high-dose MP 160 to 1000 mg/day for 5 to 14 days if patients continued to have high fever after 3 days, with pulmonary infiltrates involving more than one pulmonary segment or expanding area of consolidation. Improvements only occurred in IFN-α recipients who also received high-dose corticosteroids (Group D). In Groups A, B and C, 7.5% (3 out of 44), 6.7% (2 out of 30) and 13.3% (8 out of 60) of patients needed mechanical ventilation respectively. The mortality rates in Groups A, B and C were 5% (2 out of 40), 6.7% (2 out of 30) and 11.7% (7 out of 60) respectively. In Group D (IFN-α plus high-dose corticosteroids early when indicated), none of the 60 patients required mechanical ventilation or died.

In an open-label, retrospective and uncontrolled study from Toronto, SARS patients treated with corticosteroids plus subcutaneous IFN-alfacon-1 (n = 9) had a better clinical course in terms of need for ICU admission (33%), mechanical ventilation (11.1%) and death (0%) compared to a historic cohort that received a lower dose of corticosteroids alone (n = 13; 38.5%, 23.1% and 7.7%, respectively).[48] Their results suggested that the use of INF-alfacon-1 and steroids was associated with a shorter time to 50% resolution of lung radiographic abnormalities, better oxygen saturation level, shorter duration of supplemental oxygen therapy, lower levels of creatinine phosphokinase and a more rapid return of lactate dehydrogenase to normal.

However, in late-stage disease, 4 out of 6 critically ill patients in this cohort died despite combination therapy, implying that early treatment is important.

A placebo-controlled clinical trial of IFN-alfacon-1 is currently being developed by the Collaborative Antiviral Study Group, under the sponsorship of the National Institute of Allergy and Infectious Diseases, for patients with early SARS.[14]

**Protease Inhibitors**

Protease inhibitors block the final step of virion assembly in the treatment of human immunodeficiency virus infection with proven efficacy.[43,49] The cytopathic effect of SARS-CoV was inhibited by lopinavir at 4 ug/mL and ribavirin at 50 ug/mL after 48 hours of in vitro incubation.[50]

In a preliminary report from Hong Kong, there were no deaths at 30 days after the onset of symptoms among the 34 patients treated with Kaletra (400 mg ritonavir and 100 mg lopinavir) for 14 days in combination with ribavirin as initial therapy, compared to 10% mortality in 690 patients taking only ribavirin.[49] Delay in administering Kaletra resulted in higher mortality; 21% of 33 patients who received Kaletra as a "late rescue therapy" died, compared to 42% of 77 patients who received ribavirin alone.

In a retrospective study in Hong Kong, addition of lopinavir 400 mg/ritonavir 100 mg orally 12-hourly for 10 to 14 days as initial treatment to a standard therapy (n = 44), when compared to a matched cohort (n = 634), was associated with a reduction in the overall death rate (2.3% versus 15.6%, $P$ <0.05) and intubation rate (0% versus 11.0%), and a lower rate of use of MP at a lower mean dose (1.6 g versus 3.0 g, $P$ <0.05).[51] Patients who received lopinavir/ritonavir as a rescue therapy (n = 31) showed no difference in the overall death rate and rates of oxygen desaturation and intubation compared to the matched control (n = 343), and received a higher mean dose of MP (3.8 g versus 3.0 g, $P$ <0.05).

In a non-randomised open-label study (n = 152) in Hong Kong, Kaletra was used as initial (n = 12) and rescue therapy (n = 29) for SARS, in addition to standard therapy consisting of ribavirin and corticosteroids.[50] Compared to historical controls (n = 111) who received standard therapy, Kaletra recipients (n = 41) had a significantly lower incidence of ARDS or death (28.8% versus 2.4% respectively) at day 21 after symptom onset. The initial treatment subgroup, compared to the rescue treatment subgroup and historical control, showed a reduction in steroid usage and nosocomial infections, as well as a decreasing viral load and rising peripheral lymphocyte count. Kaletra treatment was associated with better outcome even when adjusted for baseline lactate dehydrogenase level.

The viral replicative phase peaks around day 10.[30] If available, an effective antiviral agent used within this therapeutic window would decrease the peak viral load and the associated degree of immunopathological damage. This may explain the decreased need for immuno-suppressants and the decreased risk of nosocomial infections in the above study.[50]

Adverse reactions associated with Kaletra include severe pancreatitis, diarrhoea, abdominal pain, asthenia, headache, nausea, insomnia, skin rash, liver dysfunction, and a fall in haemoglobin of >2 g/dL.[43,50]

Kaletra treatment will be used in a controlled trial in Hong Kong in case SARS recurs.[17]

**Immunoglobulins**

Immunoglobulins have immunomodulatory properties and may modify cytokine expression.[52] IV immunoglobulins have been shown to be beneficial in the treatment of many autoimmune and inflammatory conditions.[53] The higher concentration of IgM might theoretically enhance its immunomodulatory effect.[54] Significant improvement in radiographic scores and oxygen requirement after treatment with IgM-enriched immunoglobulin (Pentaglobin) (5 mg/kg daily for 3 days) were reported in 12 SARS patients from Hong Kong who did not show favorable response to treatment with rescue pulse MP and ribavirin therapy.[37] No adverse event attributable to Pentaglobin administration was reported.

IV immunoglobulins pooled from multiple donors would not be expected to contain specific SARS-CoV antibodies because of the low background immunity in the population. An uncontrolled cohort study from Singapore using combination pulse MP (200 mg daily for 3 days) and moderate dose IV immunoglobulin (0.4 g/kg body weight daily for 3 days) showed a non-significant trend towards reduced mortality without significant adverse effects in critically ill SARS patients.[55]

A double-blind placebo-controlled study using immunoglobulins alone or in combination should be undertaken to define their efficacy.[56]

**Convalescent-phase Plasma**

In SARS, like in most viral illnesses, the viral load peaks in the first week.[57] The patient then develops a primary immune response by day 10 to 14, followed by viral clearance. Convalescent plasma should be more effective when administered early in the course of the illness. This might explain the lack of effectiveness of convalescent plasma when administered after day 16.

Convalescent plasma, with high levels of anti-SARS-CoV antibodies, have been used to treat SARS in Hong Kong, China and Singapore.[43,58] In a retrospective study

from Hong Kong, 40 patients with progressive disease after ribavirin treatment and 1.5 gm of pulse MP were given either convalescent plasma (n = 19) or further pulse MP (n = 21).[57] Patients treated with convalescent plasma had a shorter hospital stay and lower mortality than their counterparts. There were concerns about the possible transmission of SARS-CoV (and other pathogens) to patients and the risk of anti-SARS immunoglobulin being pro-inflammatory, thus aggravating the pneumonitis.[43] No adverse effects of convalescent plasma were reported.[57]

The rapid depletion of convalescent plasma caused by its enthusiastic use during the epidemic and the rapid decline of anti-SARS-CoV IgG titre among SARS survivors make it difficult to conduct controlled clinical trials of this potential therapy.[43]

## Other Therapies

Plasma exchange was used as a salvage therapy in Hong Kong.[37] Other experimental treatments include glycyrrhizin (derived from liquorice roots),[27] tumour necrosis factor alpha-blockers,[15] pentoxifylline, small interfering RNAs, niclosamide, fusion inhibitors, neutralising monoclonal antibodies and traditional Chinese medicines.[14,21,31] However, there has been no systematic evaluation of their clinical efficacy, and their use is not recommended.[21]

## Conclusions

Primary antiviral prevention is not possible as there is no vaccine against SARS in humans, although vaccines exist for animal coronaviruses. Vaccine biologists have developed a prototype vaccine against a coronavirus that causes bronchitis in chickens.[59] A new vaccine for SARS is likely to appear in the near future.[60]

The natural history of untreated SARS is uncertain.[21] There were no randomised placebo-controlled trials to evaluate whether the various antivirals (e.g., ribavirin, IFN and protease inhibitors) or immunomodulatory agents (e.g., corticosteroids) were beneficial.

There are 3 identifiable pathogenic stages of SARS of varying duration, which may overlap chronologically. These stages are viral replication, inflammatory pneumonitis and residual pulmonary fibrosis.[17] Antiviral therapy may be considered during the viral replication phase. Immuno-modulation therapy such as corticosteroids should be withheld until the second week to counteract the BOOP-like phase,[40] and pulse MP for patients with clinical deterioration manifested by persistent fever, worsening radiographic opacities, and hypoxaemic respiratory failure.[14,61,62]

A few controlled clinical trials of some of these therapeutic agents have been planned in case SARS re-emerges.

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