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Review Article

# Corticosteroid Therapy for 2019 Novel Coronavirus: Lessons From SARS and MERS

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**Abstract**
For the last three decades, the world population has experienced new epidemics of coronaviruses. The world is currently witnessing the novel coronavirus disease (COVID-19) epidemic, which is a disease that comes from a novel coronavirus called Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The available genetic and clinical proofs suggest a similar route to those of Middle East respiratory syndrome (MERS) and SARS. The clinical manifestations of infections caused by coronaviruses including SARS, MERS, and COVID-19 are pneumonia, bronchitis, or other serious respiratory infections. Various transmission ways (e.g., nosocomial transmission) and transmission through moderately symptomatic or non-symptomatic infected individuals have caused great concerns. Although no certain treatment has so far been developed for this disease, and prevention is the main applied strategy for these viruses, some medications can be used to help with this disease. Corticosteroids can be mentioned as an example of these medications. This article specifically reviewed the evidence regarding the effectiveness of the corticosteroid therapy for the coronavirus family (i.e., SARS, MERS, and COVID-19) and showed that there are insufficient data to recommend corticosteroid therapy for patients suffering from COVID-19.
**Keywords:** Coronavirus, MERS virus, SARS virus, COVID-19, Corticosteroids

## Background

Since its emergence in mainland China in mid-December 2019 until 21 September 2021, the 2019 novel coronavirus (2019-nCoV) has infected more than 227 940 972 confirmed cases in 206 countries and territories around the world and caused 4 682 899 deaths (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third member of the Coronaviridae family that can cause disease (2), the most common manifestations of which are fever, cough, and fatigue (or myalgia). According to evidence (3), more severe cases are presented with pneumonia and acute respiratory distress syndrome (ARDS).

Corticosteroids are considered a class of steroidal hormones, which are commonly applied in inflammatory conditions due to their anti-inflammatory effects. According to results from previous human coronaviruses (hCoVs) such as SARS and MERS, which will be thoroughly discussed in this review, the duration, dosage, and timing of corticosteroid therapy are influential factors on the efficacy of the treatment (4).

According to the World Health Organization (WHO), using corticosteroids for nCoV-associated pneumonia (outside of clinical trials) is not recommended unless there are other indications that require the treatment (5). Corticosteroids were used during previous hCoV epidemics (SARS-CoV and MERS-CoV) and resulted in some adverse outcomes such as delayed viral RNA clearance from the blood (6-8). Similarly, steroid use in SARS-CoV patients contributed to some adverse conditions such as diabetes, psychosis, and increased risk of avascular necrosis (6,7,9). On the other hand, corticosteroid therapy showed some positive outcomes in selected SARS patients with critical conditions (10). Corticosteroid therapy was also applied for critically ill MERS patients, who demonstrated a higher chance of requiring renal replacement therapy, mechanical

ventilation, and vasopressors (8). Corticosteroid therapy has so far been applied by Chinese physicians during the current 2019-nCoV outbreak (11). However, routine corticosteroid use is not currently recommended due to the lack of enough evidence unless for patients who are critically ill and in the lowest dose and shortest time (12,13). Considering that the effects of corticosteroid therapy can be highly controversial, this review intends to clarify both beneficial and adverse effects of corticosteroids in the treatment of patients with the 2019-nCoV infection, which has become a global concern due to its ongoing outbreak.

## Etiology

SARS-CoV-2 is an enveloped non-segmented positive-sense RNA virus. Complete genome analysis for this virus revealed that there are nearly 90% and 50% similarities between SARS-CoV-2 and SARS-CoV, as well as SARS-CoV-2 and MERS-CoV genomes, respectively, causing acute respiratory disorder and ARDS (14). Four main structural proteins placed on the envelope are encoded by the SARS-CoV-2 genome. One of these proteins is spike protein binding to the angiotensin-converting enzyme 2 (ACE2) receptor, and subsequently mediating the fusion between the cell membranes of the host and the SARS-CoV-2 envelope. Then, this virus enters the host cell (15). Coronavirus spike protein consists of 2 functional subunits (i.e., S1subunit and S2 subunit), which are responsible for binding to the receptor of the host cell and mediating fusion between virus envelope and host cell membrane, respectively (16). Finally, the virus antigen is recognized by the antigen presentation cells (APCs) after the entrance of the virus into the host cell, and then the immune system responds to the antigen representation of APCs. Based on available data, bats might be considered as the initial SARS-CoV-2 host. This virus might be initially transmitted to humans through a wild animal sold at a seafood market in China and subsequently spread by human-to-human transmission (15).

## The Mechanism of Corticosteroids

Corticosteroids are highly efficient in suppressing eosinophilic inflammation in the airways in people with asthma. A rise in the transcription and expression of anti-inflammatory proteins including neutral endopeptidase, interleukin (IL)-10, and IL-1 receptor antagonist causes this anti-inflammatory effect. More notably, this effect is due to the repression of inflammatory genes including cytokines, which are associated with the inflammatory response in asthma (e.g., IL-5, IL-4, and chemokines engaged in the recruitment of eosinophil). They inhibit the activation and recruitment of inflammatory cells, specifically eosinophils, macrophages, dendritic cells, and T lymphocytes. Although they do not block the activation of mast cells, they inhibit their survival at the surface of the airway, thus preventing their activation in difficulties including exercise and fog. It is widely recognized that corticosteroids inhibit the release of mediators in the airways from structural cells, including smooth muscle, fibroblasts, endothelial cells, and epithelial. Indeed, an inhibitory effect on epithelial cells is probably one of the important actions of inhaled corticosteroids (17). Corticosteroids are the typical immunosuppressive medications that are effective in stopping or postponing pneumonia progression and are efficient in treating ARDS (18, 19). In addition to immunosuppressive actions, corticosteroids play an anti-inflammatory role in decreasing systemic inflammatory, promoting the absorption of the inflammasome, reducing exudative fluids in the lung tissue, and preventing more diffuse alveolar damage, which can avoid the progression of respiratory insufficiency (20). Nonetheless, the role of corticosteroids remains unproven. Although the WHO and current international consensus have recommended against their use, Chinese guidelines suggest short-term therapy with low to moderate corticosteroid dose in COVID-19 ARDS (21). In a study, patients with severe COVID-19 pneumonia had dramatically elevated inflammatory markers including IL-6, and C-reactive protein, indicating the circumstance of the inflammatory reaction phase. Furthermore, most patients experienced dyspnea, cough, fever, and dramatically reduced oxygen saturation, which are the early clinical manifestations of ARDS. The findings showed that early application of low-dose corticosteroids could help the treatment effect, posing as enhancement of the symptoms of hypoxia and fever, reducing the duration of the disease course, and hastening focus absorption. Due to refined management and condition monitoring, no serious problems induced by corticosteroids resulted in these cases (20). A previous autopsy study indicated that the dysregulation of cytokines may be a critical pathogenic mechanism (22). The appropriate anti-SARS treatment should include an efficient anti-SARS-CoV medication and an immunomodulating drug to lessen the extreme and dangerous immunological response (23). It has been revealed that the MERS-CoV RNA clearance was delayed by corticosteroid therapy. Corticosteroid therapy also postponed the viral clearance of SARS (7) and avian influenza A(H7N9) (24). It may be associated with the immune-suppressing effects of corticosteroid therapy that are mostly mediated by T-cell responses (7). However, it is necessary to mention that persistent MERS-CoV RNA positivity does not necessarily demonstrate the persistent shedding of the live virus (8).

## Corticosteroids and COVID-19

Currently, there is limited evidence from the randomized clinical trials from conventional medicine to support any pharmacological therapies or vaccines for COVID-19 (25-29). The use of corticosteroids during MERS-CoV and SARS- CoV epidemics had a relationship with adverse consequences such as a delay in the clearance of viral RNA from the blood (6-8). Additionally, corticosteroids have been applied in many sick people during the current

COVID-19 pandemic in China (11).

The mixture of ribavirin and lopinavir/ritonavir indicated powerful suppression on the reduction of steroid application and the viral load (30). It is proved that interferons (IFN) play a role in suppressing SARS viral replication in vitro and are also known as a helpful treatment for the novel coronavirus (6,28,31,32). The corticosteroid use during the COVID-19 pandemic has been widely reported in different studies (6,29,33-36). According to the pathological data of hyaline membrane formation and pulmonary oedema in research by Xu et al, appropriate use of the corticosteroids, along with the ventilator support must be considered for severe patients to stop the development of ARDS (37).

Similarly, Wang et al found that in cases with severe COVID-19 pneumonia, short-term, low-dose, and early use of corticosteroids was related to the faster recovery of lung injury and clinical symptoms (20).

However, recent evidence shows that the advantages of corticosteroid application are uncertain and may probably be outweighed by some side effects such as delayed osteoporosis, viral clearance, diabetes, psychosis, and avascular necrosis (8,12,38,39). By February 22, 2020, the interim of the WHO guideline did not support the employment of systemic corticosteroids for the therapy of ARDS and viral pneumonia for people suspected of COVID-19 (40).

In a previous study by Deng et al, which consisted of adults aged 18 or older, without invasive ventilation and with laboratory-confirmed COVID-19 cases, 43% of the cases of the monotherapy group received corticosteroids, 31% of whom represented improvements in their chest CT scan results on day 7. Thus, corticosteroids may not enhance the improvement of lung injury, and it was also proposed that the possibility of the safe application of corticosteroids is still unknown (6, 41).

In another cohort study, Zhou et al included all adult patients aged 18 or older with laboratory-confirmed COVID-19 who had died or had been discharged by Jan 31, 2020, in Wuhan Pulmonary Hospital (Wuhan, China) and Jinyintan Hospital. They concluded that intravenous immunoglobulin and systematic corticosteroid use varied considerably between the survivors (23%) and non-survivors (48%), and the duration and the initiation time of the use of systematic corticosteroid were similar between these two groups (42).

Currently, there is insufficient evidence to offer the routine application of corticosteroids, and its application has to be judicious in severely ill cases for the shortest time at the lowest dose (12,13).

Accordingly, the result of this paper recommends further investigations for or against the use of corticosteroids for patients with COVID-19 (11).

## Corticosteroids and SARS

SARS caused by infections with SARS coronavirus is a life-threatening disease. The early stage of this disease is probably because of the virus itself while the later stage is considered to be due to an inflammatory reaction. The quantitative reverse transcriptase-polymerase chain response of nasopharyngeal aspirates shows the viral load peak to be at approximately 10 days from the onset of symptoms (43), and the serum concentrations of IL-8, IL-6, IL-16, and tumor necrosis factor-α are found to most significantly increase 8-14 days from the beginning of the disease (44). Furthermore, cytokine dysregulation is indicated by the histological changes in the lungs of patients who died from SARS (22). Therefore, available data indicate that in the second week of the outbreak, SARS clinical manifestations are mainly triggered by an extreme immune reaction to viral infection rather than an infection itself. The intensive care unit admission happens 8-9 days after symptom initiation and its average stay time is 8.5-14.5 days (45-47). Thus, the severe respiratory failure, occurring in the later stage of SARS and causing critical diseases, seems to be triggered by an extreme inflammatory reaction to infection with the SARS coronavirus. This proposes that corticosteroids play a part in treating patients who are critically sick with SARS in order to recover the inflammatory reaction and reduce the progression to fibrosis in those with ARDS (48).

A substantial rise in IL-8, IFN-c inducible protein-10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1) was demonstrated by the chemokine profile. Corticosteroids expressively decreased IL-8, MCP-1, and IP-10 concentrations 5-8 days after treatment. The data confirmed that the Th1 cell mediates immunity and hyper innate inflammatory reaction in SARS via accumulating monocytes/macrophages and neutrophils. The necroscopic outcome of the characteristics of ARDS recommends using steroids in SARS (49). There are many reports about the successful use of steroids in treating ARDS24 and septic shock (50). However, no significant difference was discovered by Lew et al (47) among 15 patients treated with immunoglobulin and methylprednisolone and 30 with no administration of these agents. Based on a report in China (51), a regimen containing high-dose steroids is connected to decreased death. However, this research represents non-blinded assessments, biased randomization schemes, and substantial cross-over between treatment groups.

Although the applicable dose in SARS steroid treatment is unidentified, the used doses appear to vary from no therapy to pulse doses of methylprednisolone with up to 1 g/day (45,47,51,52). Ho et al (23) compared patients treated with a high dose of steroids were compared with those treated with more conventional doses of steroids (methylprednisolone < 500 mg/d) and found no significant difference in a fatality or mechanical ventilation period during 21 days. Nonetheless, they proposed the primary use of pulse methylprednisolone treatment (>500 mg/d appears) as a more effective and safer steroid regimen compared to those with lower dosages. Thus, it must be regarded as the preferred steroid regimen in SARS treatment. Furthermore, their data indicated that 4.2% of

the patients only have severe secondary infections, even though using such high-dose steroid therapy is risky, particularly for intubated patients.

However, the potential helpful effects are required to be well-adjusted against the major side effects such as nosocomial infections (53), hyperglycemia, hypertension, hypokalemia, and gastrointestinal hemorrhage (54-56). Avascular necrosis of bone (AVN) is probably the most severe medium-term side effect of steroids in patients suffering from SARS (57). Therefore, the potentiality of corticosteroids to defeat the innate host facing SARS-CoV, which results in viral replication, should be taken into account. A rise in viral load was reported by Chu et al (58) in one patient after pulse methylprednisolone treatment. SARS clinicians must generally prescribe steroids in despairing situations based on anecdotal experience and a primary understanding of the part that host inflammatory harm has in this situation.

## Corticosteroids and MERS

MERS-CoV is known as a pathogenic virus which often leads to severe acute respiratory disease, and its mortality rate is considerable and more than SARS. Its management is mostly supportive because no special therapy has already been found for this virus (59-61). Some researchers declared that steroid therapy, according to experience from SARS, may be helpful for acute MERS illness (62). However, based on studies by Martin-Loeches et al and Stockman et al, applying corticosteroid therapy on SARS and influenza patients was connected with more morbidity (6, 63), and its effect on MERS patients' outcomes is unknown (64).

Evidence on diffuse necrotizing pneumonia, alveolar damage, lobular and portal hepatitis, acute renal injury, and myositis as the result of macrophages infiltration has been indicated by a fatal case autopsy (65). Thus, a possible important factor in the pathogenesis of MERS is that MERS-CoV abnormally leads to inflammatory chemokines and cytokine induction (66). In infections by MERS and SARS, the histology of lungs showed diffuse alveolar harm and inflammation (67) and hemophagocytosis (22). Chan et al reported that the MERS-CoV replication was reduced by using IFN in ex-vivo human lung cultures, implying that immunomodulatory therapy can be effective in MERS treatment (68). Due to the potential of MERS-CoV that results in pneumonia in normal people and promotes a secondary fungal or bacterial co-infection and the disease severe stage in immunocompetent patients, corticosteroids as immunomodulatory substances (e.g., IFN) might be helpful in the treatment of ADRS caused by MERS-CoV (69).

The immune responses of the host cause ARDS and acute lung injury. Lung inflammation can be suppressed by corticosteroids, but the inhibition of immune responses and thus suppression of pathogen clearance are the other functions of corticosteroids. Treatment by corticosteroids theoretically suppresses the inflammation of the lungs (70). According to Arabi et al, because no special effective antiviral therapy has been proven against MERS, systemic therapy by corticosteroids is usually applied for critically MERS-infected patients in order to modulate the dysregulation of cytokines, even though its effect on clinical consequences is unclear (71).

Corticosteroids were applied as an adjunct therapy for many MERS cases (72,73). In a study by Al-Tawfiq et al on 5 MERS patients, three cases received adjunct steroids, as well as ribavirin and IFN (72). In another study by Arabi et al on 13 MERS cases, one person with thrombocytopenia received steroids in addition to intravenous immunoglobulin (74).

The results of an observational study by Arabi et al on 309 MERS cases indicated the more possibility of requiring vasopressors, renal replacement therapy, and ventilation among those cases receiving high doses of steroids. They also reported that 90-day crude mortality of corticosteroid receiving MERS-patients was higher than that of the comparator group (8). Accordingly, systemic corticosteroids might cause a delay in viral clearance in MERS-CoV infected patients (8). Conversely, there are some other significant complications to be considered, including hyperglycemia, neuromyopathy, and opportunistic infections, which were not examined in the above-mentioned study. Moreover, future studies are required to discover whether treatment with systemic corticosteroids causes more infectivity of hospitalized MERS-patients via viral shedding prolongation (8,75). Alfaraj et al reported that MERS patients' mortality increased by several factors, among which continuous renal replacement therapy and corticosteroids had the highest odds ratios and thus were more significant compared to other factors (76).

Therefore, given that steroid use can potentially inhibit the viral clearance and prolong the viremia period, it is controversial and is not recommended by the WHO (12). Supportive therapy remains the principal MERS treatment (61,75). The risk of applying systemic corticosteroids for the treatment of MERS patients may be more than its benefits, and they should not be used unless there are indications because they may delay the clearance of MERS-CoV (75).

## Other Therapeutic Options for COVID-19, SARS, and MERS

Because of the lack of efficient antiviral therapy for COVID-19, present treatments mainly focus on respiratory and symptomatic support. Oxygen therapy was accepted by almost all patients (77). Lopinavir/ritonavir and IFN are most likely to be effective for COVID-19 and are now evaluated in China. Among health care workers, as post-exposure prophylaxis, a lopinavir/ritonavir and ribavirin combination was used, which might have decreased the chance of infection (78). Chloroquine is a repurposed agent which is an antimalaria drug and has a high potential for COVID-19 treatment (79). Remdesivir

is also a potential agent which has a continuing trial in China. In the US, it was used in a COVID-19 case with a good result (80). Chloroquine and remdesivir combination was demonstrated to efficiently inhibit the COVID-19 in vitro (77). In addition, Western and Chinese drug treatments such as Arbidol, lopinavir/ritonavir (Kaletra®), and Shufeng Jiedu capsule (a Chinese medication) were combined by clinicians and prescribed, leading to considerable improvements in the related symptoms with pneumonia (81). Favipiravir, nitazoxanide, and nafamostat are other antiviral drugs (77). Preliminary clinical studies demonstrated that early convalescent plasma application in COVID-19 patients could expedite clinical recovery (3). Tocilizumab is a monoclonal antibody which is against the IL-6 receptor and has represented favorable preliminary clinical results. The effectiveness and safety of tocilizumab in COVID-19 infections are now examined by some researchers (82). Several drugs are suggested as other possible medicine candidates although the clinical efficacy of these medications has not yet been proved for COVID-19. According to Lai et al (83), these drugs include DNA synthesis inhibitors (e.g., tenofovir, disoproxil, and lamivudine), teicoplanin, nucleoside analogs, ACE2-based peptides, novel vinyl sulfone protease inhibitor, neuraminidase inhibitors, 3C-like protease (3CLpro) inhibitors, and Chinese traditional medicine (including Lianhuaqingwen capsules).

Currently, there is no specific antiviral drug to be efficient in randomized controlled trials, thus supportive care is the most critical treatment for MERS and SARS (84). Several IFNs have been tested both in animal models and in vitro for their antiviral effects against SARS-CoV. The most active IFN has been constantly proven to be IFN β, followed by IFN α. Lopinavir/ritonavir, human immunodeficiency viruses (HIV), and protease inhibitors were documented to decrease intubation, mortality, and methylprednisolone use when presented as a treatment in early-stage SARS cases (28,85). Depending on the wide-spectrum antiviral effect, ribavirin was also extensively used in SARS. Ribavirin and lopinavir/ritonavir combination demonstrated greater reductions of viral load and decreased steroid use. Many observational studies documenting viral etiology SAR infections have constantly recorded improved mortality after convalescent plasma receipt in different doses. Chloroquine can also decrease the release and production of factors such as IL-6 and tumor necrosis factor, which mediate viral infection inflammatory complications (86). Its anti-inflammatory characteristics can be favorable for SARS treatment (87). Preclinical results suggest the potent effectiveness of remdesivir (a wide-spectrum antiviral nucleotide prodrug) to treat SARS-CoV and MERS-CoV infections (88,89). It has been confirmed that multiple human monoclonal antibodies to the S-protein are capable of neutralizing the virus and can be beneficial for prophylactic or therapeutic uses. The use of small molecules and synthetic peptides which block the ACE2 and S protein interaction (e.g., recombinant proteins aiming the S protein heptad repeats, luteolin, quercetin, and peptides representing various ACE2 regions) is another strategy to inhibit viral entry and viral fusion (90).

In several observational studies, IFN has been employed to treat MERS-CoV and SARS-CoV patients (87). The results of a recent study revealed that both ribavirin and IFN-α2b decreased the MERS-CoV replication in LLC-MK2 cells and Vero, thus a combination of these two drugs at a minor concentration, attained the same endpoints which could ease their clinical uses (91). In plaque assays, a monoclonal antibody directed against the Ras-binding domain of MERS-CoV's S protein was shown to have neutralizing activities in vitro (92). The convalescent plasma use for the MERS-CoV treatment may be difficult in a clinical trial because of the small number of possible donors with adequate antibody titers (93). Researchers have previously reported that lopinavir and ritonavir, which are used for HIV infection treatment (94), could enhance the result in SARS-CoV (30) and MERS-CoV (95) patients. Some in vivo studies found numerous agent activities against MERS-CoV, including chlorpromazine, mycophenolic acid, chloroquine, and cyclosporine (96,97). A number of other agents are presently in a preclinical study, including chlorphenoxamine hydrochloride, fluspirilene, fluphenazine hydrochloride, thiothixene, astemizole, and promethazine hydrochloride (97).

## Conclusion

The COVID-19 pandemic has now spread worldwide, and new sights into the transmission dynamics, clinical features, pathophysiology, and management of this virus are growing. Although the coronavirus infection is highly transferable, its case mortality rate is less than MERS and SARS. Corticosteroids, which are commonly applied in inflammatory conditions, are considered as a therapy approach for coronavirus infections due to their anti-inflammatory effects. In this article, the effect of corticosteroid therapy was discussed with a review of available data from COVID-19, SARS, and MERS. There is not enough evidence to recommend the routine application of corticosteroids for COVID-19 at present and its application has to be judicious in severely ill cases for the shortest time at the lowest dose. In patients suffering from SARS, AVN was probably the most severe medium-term side effect of steroids. On the other hand, corticosteroid therapy showed some positive outcomes in selected SARS patients with critical conditions. The risk of applying systemic corticosteroids for treating MERS patients may be more than its benefits. Accordingly, they should not be used unless under specific conditions since they may delay the clearance of MERS-CoV. International and national health care agencies have so far performed coordination to control the further spread of this pandemic. Nonetheless, further international collaboration is required in this respect. Only time can define how this story will unfold from COVID-19, and more investigations are needed to

find the effective therapy for this novel type of coronavirus.

## Authors' Contribution

Study concept and design: MF and KV; Analysis and interpretation of data: ND and AT; Drafting of the manuscript: SY, EA, and MM; Critical revision of the manuscript for important intellectual content: TF and NK; Statistical analysis: KV; Study supervision: MF and ND. All authors discussed the results and contributed to the final manuscript.

## Conflict of Interests

The authors confirm that they have no conflict of interests.

## Ethical Approval

Not applicable.

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