



Calming the Storm: A review of corticosteroid use in severely ill COVID-19 patients on mechanical ventilation

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Abstract:

The importance of corticosteroids in the therapy of COVID-19 has been controversial. However, as the world develops a better understanding regarding the pathophysiology of COVID-19, we are realizing that suppressing the host immune response may reduce lung inflammation preventing further complications. In addition, more high-quality randomized controlled trials, meta-analysis, and review articles are being published discussing the role of corticosteroids. Majority of these studies concluded that corticosteroids are beneficial for hospitalized severely ill COVID-19 patients requiring supplemental oxygen.

To date, therapeutic guidelines for COVID-19 patients recommend dexamethasone or other alternative corticosteroids, including methylprednisolone, hydrocortisone, or prednisone, as a treatment choice for severely ill COVID-19 patients.

This review will discuss the pharmacology, mechanism of action, pharmacodynamics, pharmacokinetics, and benefits of corticosteroids in COVID-19 patients, and review current published clinical evidence on corticosteroids.

Keywords: Corticosteroids, COVID-19, ARDS

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Introduction

Corticosteroids have been used in the treatment of COVID-19, since the beginning of the pandemic, due to their anti-inflammatory effects and on the host immune system. It is postulated that they may help severely ill mechanically ventilated COVID-19 patients, at risk of developing lung inflammation which can lead to lung injury and multisystem organ dysfunction. The use of corticosteroids may have clinical benefits for these patients. ¹

The World Health Organization (WHO) recommends systemic corticosteroids for the treatment of patients with severe and critical COVID-19. ² The criteria include patients with COVID-19 needing mechanical ventilation (invasive or non-invasive) and who are at risk for serious complications such as severe pneumonia, acute respiratory distress syndrome (ARDS), cytokine storm syndrome, and even death.

In addition, the COVID-19 Treatment Guidelines Panel ¹ recommends the use of dexamethasone or other systemic corticosteroids for hospitalized adults with COVID-19, including patients who are hospitalized and require supplemental oxygen, oxygen delivery through a high flow device, non-invasive ventilation, or invasive mechanical ventilation (IMV) and Extra Corporeal Membrane Oxygenation (ECMO). If dexamethasone is not available, alternative glucocorticoids (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.

Data from randomized controlled trials, high-quality systematic reviews, and meta-analyses strongly support using corticosteroids in patients with COVID-19 that require oxygen support. Suppression of the overwhelming systemic inflammation, by corticosteroids, can help with the inflammatory process in oxygen-dependent or severe COVID-19 patients. ²

Therapeutically, corticosteroids are immunomodulatory drugs that help prevent and attenuate the severe hyper-inflammation process in severe COVID-19 infections. This process occurs in both tissue and systemic circulation via non-genomic and genomic effects. ³ Corticosteroids may be administered intravenously (IV) or orally in severely ill patients. ^{2,3} Most literature recommends the use of dexamethasone 6 mg daily for up to 10 days or an equivalent dose of hydrocortisone 50 mg every 8 hours, prednisone 40 mg daily, or methylprednisolone 32 mg daily (8 mg every 6 hours or 16 mg every 12 hours). ^{1,2}

Corticosteroids have been studied extensively in ARDS patients ³ and are recommended in patients with persistent or refractory moderate to severe disease, who have refractory sepsis or community-acquired pneumonia.

The anti-inflammatory, antifibrotic and vasoconstrictive effects of corticosteroids have been reported to improve outcomes in patients with ARDS. ⁴

Common recommended corticosteroid regimens for ARDS include methylprednisolone 1 mg/kg per day for 21 to 28 days or dexamethasone 20 mg IV once daily for five days, tapering to 10 mg once daily for five days. This dosing is supported by a study by Villar and colleagues, ⁵ which found that use of high dose dexamethasone in moderate to severe ARDS patients had lower 60-day all-cause mortality compared to those who received standard intensive care (21% vs. 36%, P 0.005). The primary outcome resulted in the dexamethasone group had a larger mean number of ventilator-free days than patients in the control group (mean 12.3 vs 7.5 days); between-groups difference 4.8 days [95% CI 2.57–7.03] P <0.0001. The treatment with dexamethasone had more ventilator-free days.

Mechanism of Corticosteroids

The development of severe COVID-19 is dominated by inflammatory infiltrates, diffuse alveolar damage, microvascular thrombosis, and inflammatory organ injury mediated by the host immune responses. Studies have shown that oxygen-dependent COVID-19 patients have increased acute phase reactants such as C-reactive protein and serum amyloid A.

The process of excessive immune system dysregulation and increased pulmonary endothelial and epithelial permeability leads to lung damage and the release of pro-inflammatory cytokines. ⁶ Essentially, the steroid molecule binds to glucocorticoid receptors stimulating the synthesis and release of anti-inflammatory proteins.

These agents inhibit transcription factors that control pro-inflammatory mediators such as dendritic cells, mast cells, macrophages, eosinophils, and lymphocytes. Furthermore, corticosteroids inhibit phospholipase A2, an essential factor in the production of various inflammatory mediators.

This prompts the use of corticosteroids as a treatment option which helps modulate and reduce the progress of inflammation and organ failure in hospitalized patients. ^{3,7}

Figure 1 depicts the mechanism of action of corticosteroids. Generally speaking, these drugs function as agonists at the glucocorticoid receptors and/or mineralocorticoid receptors. They are classified according to hypothalamic-pituitary-adrenal (HPA) axis suppression, mineralocorticoid activity, and potency.

Corticosteroids enter the cell to the cytoplasm and bind to the glucocorticoid receptors (GR) which is complex with heat-shock protein (hsp90). It then translocates to the nucleus where it binds to a glucocorticoid recognition element (GRE) on the 5'-upstream promoter sequences of steroid-responsive genes. The positive GRE transactivation will promote anti-inflammatory mediators while negative GRE will suppress proinflammatory mediators. Corticosteroids also bind to membrane-bound GR (mGR) where non-genomic effects occur.⁸

Pharmacokinetics and Pharmacodynamics of Corticosteroids

Due to the intracellular mechanism of action of corticosteroids, the onset of systemic corticosteroids is delayed by 3-8 hours regardless of route of administration. Due to this unique intracellular mechanism, corticosteroid duration of effect does not correlate with their duration of action. Structural modifications to the steroids can increase potency and reduce mineralocorticoid effects.⁸ Both potency and mineralocorticoid activity of corticosteroids are relative to hydrocortisone.⁷

The classification of corticosteroids is broken down into short, medium, or long acting based on the duration of action on the HPA axis. Table 1 compares various corticosteroids with respect to their pharmacokinetic and pharmacodynamic profiles and potency.

Contrasting between dexamethasone and methylprednisolone, dexamethasone is a pure glucocorticoid that affects the transcription of cytokines and glucocorticoid-induced gene transcriptions. It has higher potency due to its higher affinity

for glucocorticoid receptors, however, that lacks mineralocorticoid stimulation which has minimal effect on sodium balance and fluid volume.^{6,7} Furthermore, dexamethasone is a long-acting corticosteroid with a half-life of 36-72 hours, making it effective for daily dosing compared to hydrocortisone, which has equal affinity glucocorticoid and mineralocorticoid receptors.⁹ Thus its properties make it beneficial for managing septic shock in patients with COVID-19.¹⁰

Interestingly, methylprednisolone has been the preferred agent for corticosteroids therapy by many physicians since it achieves higher lung tissue to plasma ratios in animal models than dexamethasone, which works more efficiently for lung injury.¹⁰

In a study by Ranjbar and colleagues¹¹ which was a triple-blinded randomized controlled trial that included 86 patients hospitalized with COVID-19. This study compared the use of methylprednisolone 2 mg/kg/day or dexamethasone 6 mg/day. The mortality rates and length of hospital stay were lower in patients who received methylprednisolone.

In another study by Pinzón and colleagues,¹² 216 severely ill COVID19 pneumonia patients were given methylprednisolone 250 to 500 mg IV daily for three days, followed by prednisone 50 mg orally every day for 14 days or dexamethasone 6 mg IV daily. After completing four days of treatment, the paraclinical markers, including C-reactive protein, d-dimers, and lactate dehydrogenase, were significantly lower in the methylprednisolone group. As concluded, the mortality rate was lower in the group receiving methylprednisolone.

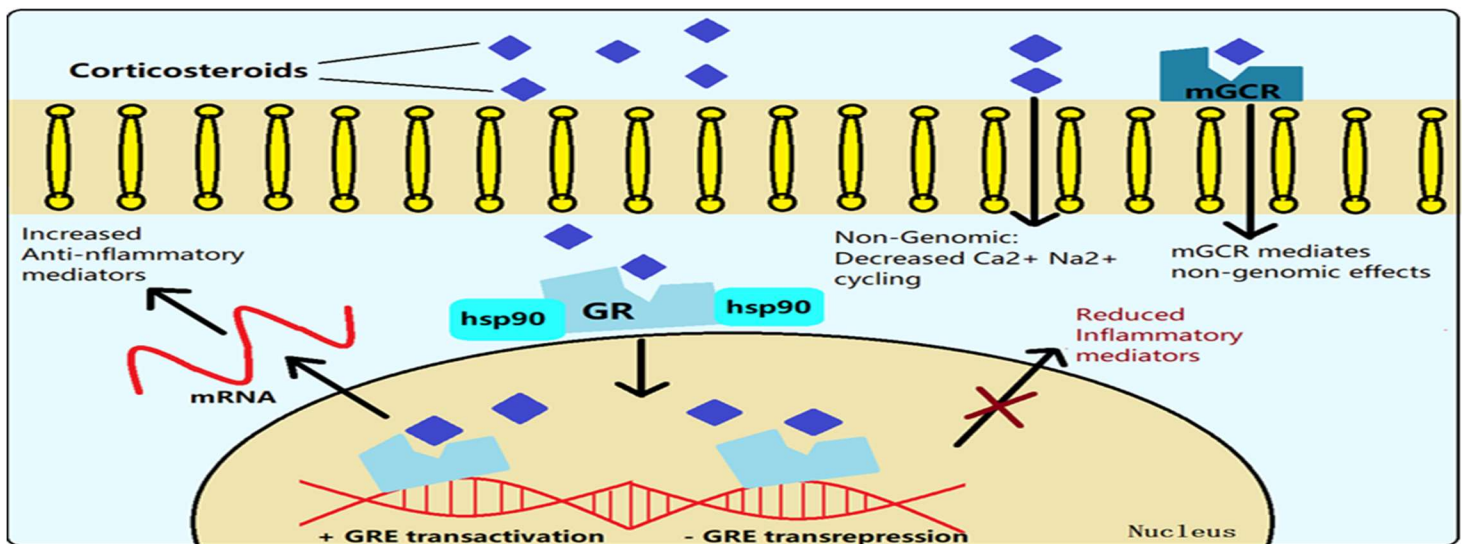


Figure 1 The mechanism of action of corticosteroids with glucocorticoid response elements (GRE) and other non-genomic effect

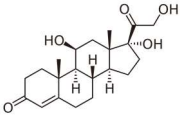
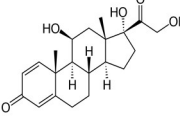
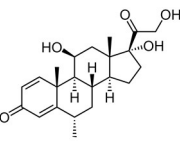
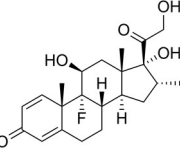
Medication	Structure	Mineralocorticoid activity (Potency relative to hydrocortisone)	Anti-inflammatory (Potency relative to hydrocortisone)	Duration of action (Hours)	Onset (Hours)	Half-Life (Hours)	Equivalent glucocorticoid dose (mg)
Short Acting							
Hydrocortisone		1	1	8-12	1	IV: 2 ± 0.3 hours; Oral: 1.8 ± 0.5 hours	20
Intermediate Acting							
Prednisone		0.8	4	12-36	Acute (minutes after administration) and/or chronic (2 to 20 hours to days)	2.1-3.5 hours	5
Methylprednisolone		0.5	5	12-36	IV (succinate): Within 1 hour	Oral: 2.5 ± 1.2 hours IV (succinate): 0.25 ± 0.1 hour	4
Long Acting							
Dexamethasone		0	30	36-54	1 hour	Oral: 4 ± 0.9 hours IV: ~1 to 5 hours	0.75

Table 1 Corticosteroid comparison chart

Corticosteroids Dosing for severe COVID-19

The National Institute of Health recommends dexamethasone for hospitalized patients requiring mechanical ventilation oral or IV 6 mg once daily for up to 10 days, alternative options including methylprednisolone 32 mg daily as a single dose or 2 divided doses, hydrocortisone 50 mg every 8 hours, or 40 mg of prednisone daily.¹

Although many guidelines recommend the previously noted standard dose of dexamethasone for critically ill COVID-19 patients, questions remain if a higher dose may benefit those with more complications due to COVID-19.

The dose of dexamethasone 6 mg/day for ten days is considered low, compared to its use in a trial done by Tomazini and colleagues (CoDEX) randomized trial¹³ in patients with moderate to severe ARDS, in which the dose of dexamethasone was 20 mg of dexamethasone IV daily for five days, then and 10 mg daily for five days or until ICU discharge was used.

A study by Fernandez-Cruz and colleagues¹⁴ concluded that an initial regimen of methylprednisolone 1 mg/kg/day of resulted in lower hospital mortalities in COVID-19 patients with pneumonia.

Another randomized clinical trial by Munch and colleagues¹⁵ completed at 26 hospitals in Europe and India assessed the effects of dexamethasone 12 mg/day versus 6 mg/day in patients with COVID-19 and severe hypoxemia. Notably, the mortality at 28 days was 27.1% and 32.3%, respectively which was not significantly different. The study also showed that there were no significant differences in days alive without life support at 28 days between the two groups.

Additionally, a meta-analysis from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group¹⁶ evaluated the daily glucocorticoid equivalent doses ranging from 6 mg to 20 mg. No differences were observed between the low versus high doses administered. Further trials will need to be conducted to compare the recommended dose to a higher dose.

Contrastingly, a pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial completed by Granholm and colleagues¹⁷ found high probabilities of benefit and relatively low probabilities of clinically significant harm with dexamethasone 12 mg versus 6 mg daily for up to 10 days in patients with COVID-19 and severe hypoxemia. The trial was an international, centrally randomized, parallel-group blinded with the inclusion of patients hospitalized with COVID-19 and severe hypoxemia, independent of the delivery system and use

of noninvasive ventilation or continuous positive airway pressure or invasive mechanical ventilation. Patients were randomized to dexamethasone 12 mg or 6 mg IV for a maximum of 10 days. The primary outcome analyzed the days alive without life support at day 28, defined as days alive without invasive mechanical ventilation circulatory support and kidney replacement therapy. The data showed an adjusted mean difference of 1.3 days and an adjusted incidence rate ratio of 1.08 with the probabilities of any benefit at 94.2% and clinically important benefits at 63.9% with 12 mg dexamethasone group at days alive without life support at day 28. The data concluded that there were high probabilities of benefits with 12 mg of dexamethasone in comparison with the current recommended dose of 6 mg.

Obesity Dosing of Corticosteroids

Aside from the questions on optimal dosing of corticosteroids in COVID-19 patients, the question of dosing in obesity also remains a debatable topic. The use of ideal or adjusted body weight is suggested for weight-based dosing in obese patients.¹⁸

Previous trials have shown that the volume of distribution of corticosteroids is closely related to ideal body weight suggesting limited distribution into adipose tissues, resulting in changes of pharmacokinetic and pharmacodynamic profiles of corticosteroids.¹⁹

A study by Dunn and colleagues¹⁹ suggests that a weight-based dose of 0.6 mg/kg IV daily, moderately obese patients with IBW over at least 35%. However, the use of an ideal or adjusted weight is suggested for weight-based dosing in obese patients with BMI of 40 kg/m² or greater is recommend for methylprednisolone for patients with ARDS.²⁰ Regardless, the dosing of corticosteroids should be adjusted based on patient-specific factors.¹³

Comparison of literature supporting the use of corticosteroids in severely ill mechanically ventilated COVID-19 patients being treated with corticosteroids

Recognizing the importance of corticosteroids in treating COVID-19, the research and investigation of corticosteroids for severe COVID-19 patients launched worldwide. As the number of critically ill patients increased, the priority of these trials is to help guide management and treatment of severely ill COVID-19 patients. The following are overview summaries of clinical studies supporting the use of various corticosteroids in the treatment of severe COVID-19 infection. These results are also summarized in Table 2.

REACT

A prospective meta-analysis of 7 randomized clinical trials that included 1,703 critically ill patients from 12 different countries.¹⁶

The trial randomized patients to receive systemic corticosteroids, including dexamethasone, hydrocortisone, or methylprednisolone in comparison to patients receiving standard care or placebo. According to the study, there were 222 deaths among 678 patients randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone and 425 deaths among 1025 patients randomized to usual care or placebo. The data resulted in an OR of 0.66 (95% CI, 0.53-0.82; $P < 0.001$) for all-cause mortality comparing corticosteroids with usual care or placebo.

The administration of systemic corticosteroids in severely ill patients with COVID-19 was associated with lower 28 days all-cause mortality compared to standard care.

Recovery Trial

A large open-label randomized control study known as the RECOVERY trial from the UK-based designed to evaluate the effects of dexamethasone treatment compared to usual care provided to hospitalized patients who were receiving oxygen without invasive mechanical ventilation.⁶ The trial enrolled 6425 patients with 2104 randomized to receive dexamethasone and 4321 randomized to receive usual care.

The treatment with dexamethasone 6 mg/d for 10 days resulted in reducing mortality by one third in patients receiving mechanical ventilated (29.3% vs 41.4%, rate ratio 0.64) and by one fifth in patients receiving supplemental oxygen (23.3% vs 26.2%, rate ratio 0.81) in comparison to usual care alone. One key difference from this trial was that there was no benefit of using corticosteroids among patients who are not on respiratory support.

Overall, the results from the RECOVERY trial demonstrated that among hospitalized patients with Covid-19, the use of dexamethasone for up to 10 days helped lower the 28-day mortality rate.

CoDEX

A multicenter, randomized open-label trial conducted in 41 intensive care units, in Brazil, on patients with moderate to severe ARDS secondary to COVID-19.¹³

The primary objective was to investigate the use of intravenous dexamethasone plus standard care in comparison to standard care alone. Patients were randomized by a 1:1 ratio

to receive dexamethasone 20 mg IV once daily for five days, then 10 mg IV once daily for an additional five days or until discharge from the ICU plus standard care, or standard care alone.

The mean number of days alive and free from mechanical ventilation during the first 28 days was significantly higher in the dexamethasone group than in the standard care group (6.6 days 95% CI, 5.0-8.2 days vs 4.0 days 95% CI, 2.9-5.4 days with 95% CI, 0.2-4.38, $P = .04$). The 28-day mortality in the corticosteroid group was 85/151 (56.3%) versus 91/148 in the no corticosteroids group (61.5% with hazard ratio, 0.97; 95% CI, 0.72 to 1.31; $P 0.85$). The number of days alive and days free from mechanical ventilation at 28 days was lower for the dexamethasone plus standard care group compared to standard care alone group. This study supported that dexamethasone may be used to attenuate lung injury in patients with COVID-19 associated ARDS. However, in contrast with the RECOVERY trial, the mortality rates were higher in the CoDEX trial.

REMAP-CAP

A multicenter, multinational, randomized trial that included 403 patients with severe COVID-19 on respiratory or cardiovascular support.²¹ Patients were randomized into three groups: fixed low-dose hydrocortisone, shock-dependent hydrocortisone, or no hydrocortisone. The clinical trial provides evidence that the treatment with hydrocortisone resulted in 93% and 80% probabilities of superiority regarding improvement in organ support-free days within 21 days compared with no hydrocortisone. The primary outcome of 28-day mortality was 78/278 in the corticosteroid versus 33/99 in the no corticosteroids group and the RR was 0.84 (95% CI: 0.60– 1.18).

However, the trial was stopped early, and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.

MetCOVID

A randomized, parallel, double-blind, placebo-controlled study in Brazil conducted among those who had clinical and/or radiological suspicion of COVID-19 and either had $SpO_2 \leq 94\%$ with room air, required supplementary oxygen, or required IMV.²²

This study was aimed to evaluate the efficacy of methylprednisolone among hospitalized patients. Patients were randomized in a 1:1 ratio to receive either methylprednisolone 0.5 mg/kg IV or placebo twice daily for five days. The primary outcome was 28-day mortality. There were 416 patients randomized, with 194 and 199 individuals

assigned to methylprednisolone and placebo groups, respectively.

The study showed no significant differences between the two groups, with an overall 28-day mortality of 38.2% in the placebo group versus 37.1% in the methylprednisolone group and OR 0.91 (95% CI 0.29-2.87). However, there was a reduced mortality rate in patients receiving steroids in patients aged over 60 years old. No evidence regarding improvement in survival in the group receiving short course intravenous MP was reported.

Mixed Results Studies

In contrast to studies supporting the use of corticosteroids in COVID-19 patients, there are also studies showing mixed results.

A study conducted by Albani and colleagues²³ concluded that treatment with corticosteroids did not affect hospital mortality in patients with COVID-19.

The results showed that 171 patients died (30.6%) with corticosteroids, and 183 patients died (21.7%) without corticosteroid treatment.

Additionally, a randomized trial done by Jeronimo and colleagues²² looking at methylprednisolone use, resulted in a 28-day mortality of 76/199 (38.2%) in the placebo group versus 72/194 (37.1%) in the methylprednisolone group (P 0.629) group showing no difference in mortality between the two groups. The results from this study provide no support for corticosteroids in improving the survival rate for hospitalized COVID-19 patients.

Studies	Design Location	Eligibility Criteria	Population Actual (n)	Corticosteroid (Drug Name)	Dose/ route/ frequency	Duration	Primary outcome with statistics
REACT ¹⁶	12 countries	Randomly assigned critically ill patients to corticosteroids group or a standard care/placebo	1703	Dexamethasone, Hydrocortisone, or Methylprednisolone	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d 6 mg/d orally or intravenously Continuous intravenous infusion × 8 d or 14 d (200 mg/d × 4 d or 7 d; 100 mg/d × 2 d or 4 d; 50 mg/d × 2 d or 3 d 200 mg/d intravenously × 7 d (continuous or bolus 50 mg intravenously every 6 h×7d 40 mg intravenously every 12 h×5d	Varies depending on trials	All-cause mortality at 28 days after randomization OR: 0.66 (95% CI, 0.53-0.82; P < .001) for all-cause mortality comparing corticosteroids with usual care or placebo
Recovery ⁶	Multicenter, randomized Non blinded Country: UK	Intubation Suspected or confirmed COVID-19	6425	Dexamethasone	6 mg/d orally or intravenously	5-10 days	28-day mortality: Corticosteroid: 428/2104 (22.9%) No corticosteroids: 1110/4321 (25.7%)

							(Age-adjusted rate ratio = 0.83; 95% CI: 0.75–0.93)
CoDex ¹³	Multicenter, Randomized Non blinded Country: Brazil	Confirmed COVID-19 Intubation Mechanical Ventilated Moderate to severe ARDS per Berlin criteria Onset of ARDS < 48h	256	Dexamethasone	20 mg/d intravenously for 5 days and then 10 mg/d intravenously for 5 days Control: standard care	10 days	28-day mortality Corticosteroids: 85/151 (56.3%) No corticosteroids: 91/148 (61.5%) RR=0.86, 95% CI: 0.64–1.15
REMAP-CAP ²¹	Multicenter, randomized Non blinded Country: Europe, USA, Canada, Australia, New Zealand, Saudi Arabia	Probable or confirmed COVID-19 Admitted to ICU receiving high-flow nasal oxygen with FIO ₂ ≥ 0.4 at ≥ 30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors	403	Hydrocortisone	Intravenously fixed 7-day course of 50 mg or 100 mg every 6 h) OR shock-dependent course of 50 mg every 6 h when shock was clinically evident) Control: standard care	7 days	28-day mortality Corticosteroids: 78/278. No corticosteroids: 33/99 RR = 0.84, 95% CI: 0.60–1.18
MetCOVID ²²	Multicenter, Randomized, Double-blinded Placebo Country: Brazil	Suspicion of COVID-19, SpO ₂ ≤ 94% with room air, required supplementary oxygen, or required invasive mechanical ventilation	393	Methylprednisolone	intravenous sodium succinate methylprednisolone 0.5 mg/kg twice daily for 5 days Control: saline solution twice daily for 5 days		28-day mortality methylprednisolone: 72/194 (37.1%) Placebo: 76/199 (38.2%) OR= 0.91 95%CI: (0.29–2.87)

Table 2 Summary of clinical trials supporting the use of corticosteroids in severely ill COVID-19 patients

Abbreviations: RECOVERY, Randomized Evaluation of COVID-19 Therapy; CoDEX, COVID-19 Dexamethasone; COVID-19, coronavirus disease 2019; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired; Methylprednisolone as Adjunctive Therapy for Patients Hospitalized with Coronavirus Disease 2019; ARDS: Acute respiratory distress syndrome; MV: Mechanical ventilation; Exp: Experimental group; OR: Odd ratio; CI: Confidence interval.

Conclusion

The recommendations of corticosteroid use in severely ill mechanically ventilated patients with COVID-19 have been challenging to decipher and the efficacy of these drugs remains controversial. The pathophysiologic processes of COVID-19 infection involve various mechanisms that cause the deregulation of immune host response, resulting in systemic inflammation.

Many guidelines recommend using corticosteroids for severely ill oxygen-dependent COVID-19 patients, given their benefits of increased chance of survival and relief from life-supportive therapy. However, there is no one specific type or dosage recommendation of corticosteroid recommended for all patients.

More high-quality studies examining and comparing the different doses, duration and classes of corticosteroids are needed to develop strong recommendations to optimize care for severely ill mechanically ventilated COVID-19 patients.

Until then, use of corticosteroids in these patients should continue to be based on the severity of illness and patient-specific factors. The optimal corticosteroids dosing and appropriate duration for COVID-19 patients still vary and need further investigation.

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