Clinical Critical Care

E-ISSN 2774-0048

VOLUME 31 NUMBER 1

JANUARY-DECEMBER 2023

Clinical Critical Care
eISSN 2774-0048

Clinical Critical Care
Volume 31, Article ID e0010, 6 pages
https://doi.org/10.54205/ccc.v31.259411

REVIEW

Rational use of corticosteroid treatment in the early phase of severe COVID-19

Anutr Thitayanapong[1, 2], Ranistha Ratanarat[1]

[1]Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, 10700
[2]Udon Thani Hospital, Udon Thani, Thailand, 41000

OPEN ACCESS
Citation:
Thitayanapong A, Ratanarat R. Rational use of corticosteroid treatment in the early phase of severe COVID-19. Clin Crit Care 2023; 31: e0010.

Received: September 23, 2022
Revised: November 9, 2022
Accepted: June 5, 2023

Data Availability Statement:
The data and code were available upon reasonable request (Ranistha Ratanarat, email address: ranittha@hotmail.com)

Funding:
No funding support.

Competing interests:
No potential conflict of interest relevant to this article was reported.

Corresponding author:
Ranistha Ratanarat
Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, 10700
Tel: (+66) 2-419-8534
Fax: (+66) 2-418-8597
E-mail: ranittha@hotmail.com

ABSTRACT:

Mechanisms of hypoxemia in COVID-19 pneumonia include pulmonary inflammation, alveolar collapse, atelectasis, and pulmonary intravascular coagulopathy due to a hyperinflammatory response to SARS-CoV-2 infection. Systemic corticosteroids are widely applied as a standard treatment for hospitalized COVID-19 patients after several studies have shown favorable outcomes. However, the standard dosing and tailoring of corticosteroids in COVID-19 patients have not been established. Differences in dosing and timing of corticosteroid use may affect the outcome of COVID-19 patients. Inappropriate use of corticosteroids can lead to less benefit and potentially harmful adverse events. Dexamethasone is the most widely used corticosteroid as a result of the positive outcome from the RECOVERY study and its high anti-inflammatory potency. Although several studies have shown the benefit of higher dose corticosteroids in severe COVID-19 patients, serious adverse events associated with the use of corticosteroids, such as superimposed bacterial and/or fungal infections, have also been observed. Therefore, in this article, we reviewed current evidence of corticosteroid usage in COVID-19 patients and suggested a strategy for tailoring corticosteroid usage according to the clinical severity and risk of the patients.

Keywords: COVID-19, SARS-CoV-2, Corticosteroid, Critical ill, Immunomodulator

INTRODUCTION

The COVID-19 pandemic has globally affected management in an intensive care unit (ICU), especially in middle-income countries [1]. After the RECOVERY trial [2] was published, corticosteroids have become one of the standard treatments for hospitalized COVID-19 patients in many guidelines [3]. Various studies on corticosteroid effects in COVID-19 patients have been published following the RECOVERY trial [4].

Hypoxemia, the hallmark of severe COVID-19 pneumonia, is caused by pulmonary inflammation, alveolar collapse, atelectasis, and pulmonary intravascular coagulopathy from immunothrombosis [5,6]. COVID-19 pneumonia often progresses to COVID-19-associated acute respiratory distress syndrome (C-ARDS) and may progress into lung fibrosis. Among survivors of COVID-19, those who had an increased inflammatory reaction, shown as an increase in inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), were likely to develop pulmonary fibrosis [7]. The concentrations of proinflammatory mediators such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6, were higher in COVID-19 patients admitted into the ICU compared to non-ICU patients and were related to an increase in severity and mortality [8–10]. Though the concept of a cytokine storm in COVID-19 is still controversial due to the varying

cytokine levels in COVID-19 patients [11,12], the hyperinflammatory model of COVID-19 has been reported in several studies [5,13]. These pathophysiologic features of COVID-19 associated with immune responses led to the rational use of immunomodulatory treatments in COVID-19 patients [2].

The model for the early phase of SARS-CoV-2 infection comprises 3 phases. (1) the early infection phase, in which the virus multiplies, resulting in viral prodrome and lymphopenia. (2) In the pulmonary phase, which marks the host response to viral infections and inflammation, anti-inflammatories are potentially beneficial for hypoxemic patients. And (3) the hyperinflammatory phase, which causes pulmonary and extrapulmonary inflammation due to multiple proinflammatory mediators [14].

The use of corticosteroids in non-COVID-19 acute respiratory distress syndrome (ARDS) has been studied before the COVID-19 pandemic and has shown some benefits [15–17]. Corticosteroids inhibit the synthesis of cytokines and inflammatory mediators via changes in gene expression through glucocorticoid receptors. Though corticosteroids have been widely used, the types, doses, and duration of the treatment in practice are still being discussed due to differences in pharmacokinetics and the long-term side effects of steroids [18,19]. Therefore, in this article, we review the literature on strategies to use corticosteroids in COVID-19 patients and demonstrate our current practice.

KEY MESSAGE:

- Although the COVID pneumonia associated with hyperinflammatory responses. A strategy for tailoring corticosteroid depended on individual patient based on balancing clinical severity and risk of complications.

CURRENT EVIDENCE

Several studies on the impact of corticosteroids on COVID-19 patients have been published. We summarized the landmark randomized controlled trials (RCTs) for various types and doses of corticosteroids in Table 1.

Type of corticosteroids

Several types of immunomodulatory agents have been studied for the treatment of COVID-19. Systemic corticosteroids are the most common medications studied due to their availability and known anti-inflammatory properties [18,19]. Differences in potency and duration of the immune-modulating effect, including potential lung penetration properties, may affect the choice of types of corticosteroids.

Dexamethasone has a longer duration of therapeutic effect and higher anti-inflammatory potency compared to other systemic corticosteroids [18]. Before the COVID-19 pandemic, dexamethasone was found to be effective in reducing the duration of mechanical ventilation and overall mortality in non-COVID-19 ARDS [16]. In the RECOVERY trial, daily 6 mg of dexamethasone for 10 days has been associated with reduced 28-day mortality, duration of hospitalization, and progression to mechanical ventilation [2]. Of note, no survival benefit was found in cases without oxygen support (Table1). The CoDEX trial hypothesized that a higher dose of dexamethasone provided clinical benefits in critical COVID-19 patients with moderate-severe ARDS receiving mechanical ventilation (Table 1). Though there was no significant mortality outcome, the number of days alive and ventilator-free was significantly higher in the dexamethasone group [20].

Methylprednisolone has an intermediate duration of effect and anti-inflammatory potency. Evidence suggests that methylprednisolone has higher lung penetration than prednisolone and dexamethasone [26,27]. In the Metcovid trial, 0.5 mg per kg of methylprednisolone twice daily did not improve survival. However, there were mortality benefits in patients from the ages of 60 and older in post-hoc analysis [23]. A higher dose of methylprednisolone has also been studied. Edalatifard et al. compared methylprednisolone 250 mg for 3 days with placebo in patients with COVID-19 pneumonia who had SpO_2 of less than 90% without mechanical ventilation [24]. The study showed significant improvement in 28-day mortality (6% vs. 43% in the control group). Importantly, they excluded the patients with evidence of bacterial infection (high procalcitonin levels). Some experts argue that the mortality in the control group was very high, even when cases with moderate to severe ARDS (SpO_2 < 75%) were excluded [24].

A few small studies compared methylprednisolone with dexamethasone in severe COVID-19 patients, defined as COVID-19 patients with hypoxemia, showing potential benefits in reducing mortality, disease progression, and recovery time. Therefore, methylprednisolone may have the potential to be the primary treatment for severe COVID-19, but a larger study may be required [27,28].

Hydrocortisone has low anti-inflammatory potency and a short-duration effect, but a higher mineralocorticoid effect, and thus has been used in refractory septic shock [29]. There has been a study showing the benefits of hydrocortisone in improving pulmonary physiology and reducing organ support [15]. Several studies have shown the potential benefits of hydrocortisone in reducing severity in severe COVID-19 patients [21,22,30].

A few studies on inhaled corticosteroids in non-severe COVID-19 patients have been done. The results showed promising efficacy in preventing hospitalization and severe disease [31,32]. However, the efficacy in hospitalized COVID-19 has not yet been studied.

Dosage of corticosteroids

The current recommended dose of systemic corticosteroids in the standard guidelines is 6 mg of dexamethasone intravenously, as published in the RECOVERY trial. However, the current practices vary, partly due to

Table 1. Randomized controlled studies of corticosteroid treatment in patients with COVID-19.

Baseline	RECOVERY NEJM 2021 [2]	CoDEX JAMA 2021 [20]	CAPE COVID JAMA 2020 [21]	REMAP-CAP JAMA 2020 [22]	Metcovid CID 2020 [23]	Edalatifard et al. Eur Resp J 2020 [24]	COVID STEROID 2 JAMA 2021[25]
N	6,425	299	149	384	393	68	1000
Type & Doses	Dexamethasone 6 mg IV or PO up to 10 days	Dexamethasone 20 mg IV x 5 days then 10 mg IV x 5 days or until ICU DC	Hydrocortisone 200 mg x 7 days 100 mg x 4 days 50 mg x 3 days	Hydrocortisone 50 mg IV q 6 hours x 7 days or up to 28 days for shock	Methylprednisolone 0.5 mg/kg IV q 12 hours x 5 days	Methylprednisolone 250 mg IV OD x 3 days	Dexamethasone 12 mg IV OD vs Dexamethasone 6 mg IV OD up to 10 days
Patients	All hospitalized	MV within 48 hours + Mod-severe ARDS (PF<200)	MV or PF <300 with HFNC/Mask	MV/HFNC/NIV/ Vasopressor	SpO_2 ≤ 94% (RA)/ On O_2/MV	SpO_2 <90%, CRP > 10 mg/L, IL-6 > 6 pg/ml	Need O_2 flow rate ≥ 10 LPM, NIV/CPAP, IMV
Median treatment duration, d (IQR)	7 days (3-10)	10 days (6-10)	10.5 days (6-14)	7 days (6-8) & 3 days (1-4) for shock			10 days
DOS at randomization, d (IQR)	8-9 days (5-13)	9-10 days (6-12)	9-10 days (7-12)		13 days (9-16)	6.8 days (+- 3)	9 days
Mean age, year	66	61	62	60	55	58.5	65
Baseline O_2 Support	60%	100% MV	100% HFNC 13% Mask with bag 6%	99.8%	47.8% (Non-invasive O_2)	100% Cannula 21%, Mask 40.3%, NIV 37.1%	O_2: 55% vs 53% NIV/CPAP: 24% vs 26%
Baseline MV	16%	100%	81%	55%	33.8%		22% vs 20%
CRP, mg/L			154 vs 185		68	96	
PF ratio		131	130 vs 133	149 vs 137	158		
Other		PF Ratio < 100 71.5% vs 73.0%		3 groups Fix-dose vs Shock dose vs No hydrocortisone			
Primary Outcome	**28-day mortality**	**Ventilator-free day at day 28**	**Death/MV/HFNC at day 21**	**RS & CVS support free at day 21**	**28-day mortality**	**Time to clinical improve or DC or death**	**Days alive without life support (IMV, Circulatory, RRT)**
Primary Outcome (Results)	**22.9% vs 25.7% (P<0.001)**	**6.6 vs 4.0 days (P=0.04)**	**42.1% vs 50.7% (P=0.29)**	**0 days vs 0 days vs 0 days**	**37.1% vs 38.2% (P=0.63)**	**11.8 days vs 16.4 days (P=0.01)**	**22 days vs 20.5 days (P=0.07)**
28-day mortality	22.9% vs 25.7% (P<0.001)	56.3% vs 61.5% (P=0.85, HR 0.97)	21-day 14.7% vs 27.4% (P=0.05)	In-hospital 30% vs 26% vs 33%	37.1% vs 38.2% (P=0.63)	5.9% vs 42.9% (P<0.001)	27% vs 32% (P=0.10)
Ventilator-free day at day 28		6.6 vs 4.0 days (P=0.04)	21-day IMV 22.7% vs 23.3%				23 vs 22 days

Abbreviations: ARDS: Acute respiratory distress syndrome; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; CVS: Cardiovascular; d: day(s); DC: discharge; DOS: Days of symptom onset; HFNC: High-flow nasal cannula; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; IV: Intravenous; MV: Mechanical ventilation; NIV: Non-invasive mechanical ventilation; OD: once daily; PF: PaO_2/FiO_2; O_2: Oxygen; PO: per oral; q: every; RRT: renal replacement therapy; RS: respiratory

different disease severity and the availability of other immunomodulatory agents such as interleukin-6 (IL-6) receptor antagonists or Janas kinase (JAK) inhibitors. The study comparing the efficacy of standard-dose versus higher-dose dexamethasone in severe COVID-19 patients showed trends to favor a higher dose of corticosteroids [25,33]. The predefined subgroup analysis demonstrated better survival in the higher-dose dexamethasone group, which was not receiving IL-6 receptor antagonists [33]. The study on higher-dose pulse methylprednisolone also showed promising results compared with the study of lower-dose methylprednisolone [23,24,28,34]. Therefore, tailoring doses of corticosteroids to the severity of the patients' conditions may provide better clinical outcomes and prevent adverse events from corticosteroids.

Timing and duration of corticosteroids

Systemic corticosteroids administered to COVID-19 patients aim to reduce the inflammatory response and the severity of the disease. Given too early, when the patients do not have systemic inflammation, it may have no benefit and lead to adverse superimposed infections and prolonged viral shedding [35–37]. In the subgroup analysis of the RECOVERY trial, corticosteroids given to patients not receiving oxygen therapy or mechanical ventilation had no beneficial outcome. Most of the following studies of systemic corticosteroids only enrolled patients with oxygen therapy or respiratory support. Another factor is the number of days since symptom onset. In most studies, the average time to initiate systemic corticosteroids is between 7-10 days since symptom onset. Therefore, as per current evidence, systemic corticosteroids should only be administered to COVID-19 patients requiring oxygen therapy or respiratory support approximately 7 to 10 days after symptom onset. Too early or too late initiation of systemic corticosteroids may have less benefit and more adverse effects. There is no standard duration for systemic corticosteroid treatment in COVID-19 patients. The duration of the studies varies from 3 to 14 days can be administered for up to 28 days if there is a concurrent shock. Therefore, adjustment of treatment duration should be individualized according to patients' severity and potential risk for adverse events from corticosteroid treatment. Tapering off corticosteroids after clinical improvement may also be used to prevent further immunosuppression by corticosteroids [18].

Potential harm of corticosteroids

Several observational studies have reported serious adverse events from corticosteroids used in COVID-19 patients. As mentioned above, systemic corticosteroid use may cause prolonged SARS-CoV-2 viral shedding [37]. One of the most serious complications is a fungus infection. Corticosteroid use has been reported as an independent risk factor for invasive pulmonary fungal infections, including mucormycosis and pulmonary aspergillosis [38,39]. Use of methylprednisolone has also been reported as an independent risk factor for ICU-acquired bloodstream infection [40]. Hyperglycemia has been frequently found in critical COVID-19 patients. Corticosteroid use can be a factor causing hyperglycemia and new-onset diabetes mellitus in COVID-19 patients [41]. In most of the studies, patients with invasive fungal infections, active tuberculosis, uncontrolled diabetes mellitus, uncontrolled hypertension, and pregnancy were included; hence, the use of corticosteroids in these populations should be aware of its potential harm [20,23,25,27]. In summary, the administration of systemic corticosteroids should be tailored to each patient to reduce the risk of potential harm to the patient, with concurrent monitoring of potential adverse effects of corticosteroids.

OUR CURRENT PRACTICE

In our center, a clinical guideline has been developed to guide the physician in steroid tailoring according to patients' severity and risk factors. A flow diagram outlining a decision-making algorithm for the adjustment of corticosteroids and other immunomodulating agents in COVID-19 patients is presented in Figure 1.

Initiation of systemic corticosteroids should be required only when the patient has resting and/or exercise-induced hypoxemia requiring oxygen therapy. The initial dose recommended is 6 mg orally or 4 mg twice daily of dexamethasone orally (Figure 1). Due to limited

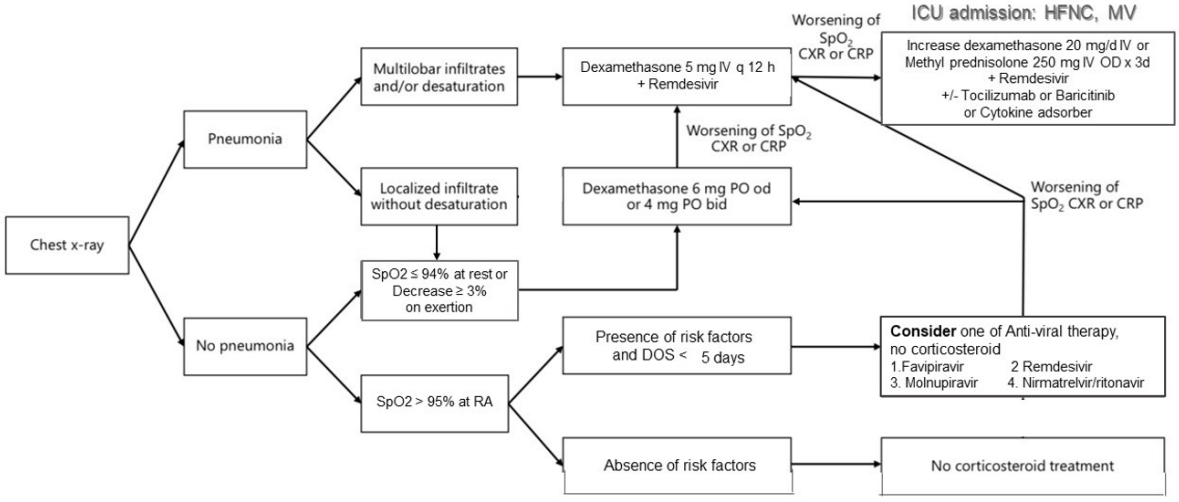

Figure 1. Flow diagram for adjustment of immunomodulating agents in COVID-19 patients. [Adapted from algorithm for COVID-19 treatment, Division of infectious disease and tropical medicine, Faculty of Medicine Siriraj Hospital, Mahidol University]
Abbreviations: CRP: C-reactive protein; CXR: Chest X-ray; DOS: Day of symptom; IV: Intravenous; OD: Once daily; PO: Per oral; RA: Room air; SpO_2: Peripheral oxygen saturation.

resources, like in other middle-income countries, a higher dose of corticosteroid can also be administered if the patient's clinical condition progresses to severe hypoxemia or is critically ill.

C-reactive protein (CRP) is being used in conjunction with clinical context to adjust the dosage of corticosteroids. Rising CRP with clinical worsening or progression of pulmonary infiltration even after initiation of low-dose corticosteroids raises the need for further management. Serum procalcitonin is applied to monitor for superimposed bacterial infections. If bacterial infection has been excluded, corticosteroid dosage should be increased; in the CoDEX trial, 20 mg of intravenous dexamethasone was recommended. Alternatively, 1 mg/kg of methylprednisolone for 5 days or 250 mg of methylprednisolone for 3 days can also be used if the risk of bacterial infection is low. These dosages are also being recommended if the presenting clinical characteristics of the patients are severe. Concurrently, one of the IL-6 receptor antagonists, JAK inhibitors, or cytokine antagonists is provided as an adjunctive immunomodulation (Figure 1).

Tapering off corticosteroids is recommended if clinical improvement has been detected. The SpO_2/FiO_2 ratio, PaO_2/FiO_2 ratio, and chest X-ray improvement should lead to a decrease in the dosage of corticosteroids. Stepwise tapering by decreasing 5 mg of intravenous dexamethasone every 2-3 days can be used if the clinical improvement is not dramatic. The total duration of corticosteroid treatment should not be longer than 10 days. Clinical worsening during corticosteroid tapering may warrant further investigation. Possible causes of clinical worsening could be too rapid corticosteroid tapering, superimposed bacterial or fungal infection, organizing pneumonia, or pulmonary embolism, depending on the clinical findings and timing of such findings.

CONCLUSION

Currently, corticosteroids are widely used in hospitalized COVID-19 patients. However, the standard of tailoring the regimen to patients' severity is not implied. Inappropriate dose, timing, and duration of corticosteroid administration can lead to less benefit and more adverse outcomes. In this article, we reviewed studies on systemic corticosteroids used in COVID-19 patients and proposed our approach to tailoring corticosteroids in the early phase of COVID-19 patients.

REFERENCES

1. Ratanarat R, Sivakorn C, Viarasilpa T, et al. Critical care management of patients with COVID-19: Early experience in Thailand. Amer J Trop Med Hygiene. 2020;103(1):48–54.
2. Dexamethasone in Hospitalized Patients with Covid-19. New England J Medicine [Internet]. 2021;384:693–704. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2021436.
3. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health.
4. Sterne JAC, Murthy S, Diaz J v., et al. Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330-1341.
5. Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med. 2021;9(6):622-642.
6. McGonagle D, Bridgewood C, Meaney JFM. A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19. Lancet Respir Med. 2021;9(6):665-672.
7. Yu M, Liu Y, Xu D, et al. Prediction of the development of pulmonary fibrosis using serial thin-section ct and clinical features in patients discharged after treatment for COVID-19 pneumonia. Korean J Radiol. 2020;21(6):746-755.
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
9. Balnis J, Adam AP, Chopra A, et al. Unique inflammatory profile is associated with higher SARS-CoV-2 acute respiratory distress syndrome (ARDS) mortality. Am J Physiol Regul Integr Comp Physiol. 2021;320(3):R250-R257.
10. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-848.
11. Kox M, Waalders NJB, Kooistra EJ, et al. Cytokine Levels in Critically Ill Patients with COVID-19 and Other Conditions. JAMA. 2020;324(15):1565-1567.
12. Sinha P, Matthay MA, Calfee CS. Is a "cytokine Storm" Relevant to COVID-19? JAMA Intern Med. 2020;180(9):1152-1154.
13. Hojyo S, Uchida M, Tanaka K, et al. How COVID-19 induces cytokine storm with high mortality. Inflamm Regen. 2020;40:37.
14. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5):405-407.
15. Tongyoo S, Permpikul C, Mongkolpun W, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: Results of a randomized controlled trial. Crit Care. 2016;20(1):329.
16. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020;8(3):267-276.
17. Chaudhuri D, Sasaki K, Karkar A, et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. Intensive Care Med. 2021;47(5):521-537.
18. Williams DM. Clinical pharmacology of corticosteroids. Respir Care. 2018.63(6):655-670.
19. Rhen T, Cidlowski JA. Antiinflammatory Action of Glucocorticoids — New Mechanisms for Old Drugs. New England J Medicine. 2005;353(16):1711-23.
20. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients with Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. 2020;324(13):1307-1316.
21. Dequin PF, Heming N, Meziani F, et al. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support among Critically Ill Patients with COVID-19: A Randomized Clinical Trial. JAMA. 2020;324(13):1298-1306.
22. Angus DC, Derde L, Al-Beidh F, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients with Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324(13):1317-1329.
23. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. Clin Infect Dis. 2021;72(9):e373-e381.
24. Edalatifard M, Akhtari M, Salehi M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: Results from a randomised controlled clinical trial. Eur Respir J. 2020;56(6):2002808.
25. Munch MW, Myatra SN, Vijayaraghavan BKT, et al. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive without Life Support in Adults with COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. JAMA. 2021;326(18):1807-1817.
26. Vichyanond P, Irvin CG, Larsen GL, et al. Penetration of corticosteroids into the lung: Evidence for a difference between methylprednisolone and prednisolone. J Allergy Clin Immunol. 1989;84:867-73.
27. Ranjbar K, Moghadami M, Mirahmadizadeh A, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. BMC Infect Dis. 2021;21(1):337.
28. Pinzón MA, Ortiz S, Holguín H, et al. Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia. PLoS One. 2021;16(5):e0252057.
29. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-1247.
30. Munch MW, Meyhoff TS, Helleberg M, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: The COVID STEROID randomised, placebo-controlled trial. Acta Anaesthesiol Scand. 2021;65(10):1421-1430.
31. Ramakrishnan S, Nicolau D v., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med. 2021;9(7):763-772.

32. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet. 2021;398(10303):843-855.
33. Granholm A, Munch MW, Myatra SN, et al. Dexamethasone 12 mg versus 6 mg for patients with COVID-19 and severe hypoxaemia: a pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial. Intensive Care Med. 2021;48(1):45-55.
34. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. GLUCO-COVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. Wien Klin Wochenschr. 2020;133(7-8):303-311.
35. Angriman F, Ferreyro BL, Burry L, et al. Interleukin-6 receptor blockade in patients with COVID-19: placing clinical trials into context. Lancet Respir Med. 2021;9(6):655-664.
36. Tang X, Feng YM, Ni JX, et al. Early Use of Corticosteroid May Prolong SARS-CoV-2 Shedding in Non-Intensive Care Unit Patients with COVID-19 Pneumonia: A Multicenter, Single-Blind, Randomized Control Trial. Respiration. 2021;100(2):116-126.
37. Li TZ, Cao ZH, Chen Y, et al. Duration of SARS-CoV-2 RNA shedding and factors associated with prolonged viral shedding in patients with COVID-19. J Med Virol. 2021;93(1):506-512.
38. Fekkar A, Lampros A, Mayaux J, et al. Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU. Am J Respir Crit Care Med. 2021;203(3):307-317.
39. Al-Tawfiq JA, Alhumaid S, Alshukairi AN, et al. COVID-19 and mucormycosis superinfection: the perfect storm. Infection. 2021;49(5):833-853.
40. Giacobbe DR, Battaglini D, Ball L, et al. Bloodstream infections in critically ill patients with COVID-19. Eur J Clin Invest. 2020;50(10):e13319.
41. Khunti K, del Prato S, Mathieu C, et al. COVID-19, Hyperglycemia, and New-Onset Diabetes. Diabetes Care. 2021;44(12):2645-2655.