Corticosteroid Therapy for COVID-19 Infection

QUESTIONS

1. In patients who have COVID infection and do not have ARDS, can corticosteroid treatment prevent ARDS?
2. In patients who have ARDS and COVID infection, do corticosteroids improve outcomes?

RATIONALE AND BACKGROUND

When associated with ARDS, COVID-19 has a high mortality rate associated with the reported phenomenon of "cytokine storm," a hyperinflammatory state that is characterized by fulminant multi-organ failure and elevation of cytokine levels. Immunosuppressive agents, including corticosteroids, have been used in COVID-19 patients to prevent or ameliorate this condition. However, the window in which steroids might be beneficial to patients with COVID-19 is not known, and experience with steroids in other severe infections may not be directly applicable to COVID-19.

CURRENT GUIDANCE (SEE TABLE 2)

1. Currently, the WHO,[1] CDC,[2] and SCCM[3] recommend against routine use of corticosteroids in patients with COVID-19 and respiratory failure who do not have ARDS.
2. SCCM/Surviving Sepsis guidelines suggest using low-dose steroids (hydrocortisone 200mg/day) for adults with COVID-19 and refractory shock. This "weak" recommendation is based on very low quality evidence.
3. SCCM/Surviving Sepsis also suggest using corticosteroids in the sickest mechanically ventilated adults with COVID-19 and ARDS. This is also a "weak" recommendation—some panelists disagreed and the evidence is not strong.[4]

CURRENT EVIDENCE (BEFORE COVID-19)

Guidance relies heavily on recent systematic reviews, including:

1. A systematic review of septic shock patients (not with COVID-19) indicating that low-dose steroids reduced ICU length of stay,[5] although there were no improvements in short- or long-term mortality. There are no studies of the use of corticosteroids in COVID-19 patients who are in shock.
2. For ARDS, Surviving Sepsis' weak recommendation to use low-dose steroids was based on updated Cochrane reviews of pharmacological agents for adults with ARDS[4] and of influenza.[6] They also found a recent multicenter RCT of dexamethasone (20 mg initial dose) in 277 ARDS patients (not COVID-19) in 17 intensive care units in Spain. Dexamethasone increased ventilator-free days and reduced mortality at 60 days.[7] However, as they note, these studies did not focus on ARDS in viral illnesses; steroid use might increase viral shedding, a potential indicator of viral replication; and ARDS might respond differently in COVID-19 than in other conditions.
3. In general, Chinese guidelines recommended wider use of low-dose glucocorticoids than other guidelines. This accounts in part for the high rate of steroid use in the case series from Wuhan described below.

NEW EVIDENCE (COVID-19 STUDIES)

In February 2020, an editorial in the *Lancet* argued that steroids were unlikely to be helpful in COVID-19 because they were not helpful in previous outbreaks (mainly SARS-CoV).[8] Since then, 4 studies of COVID-19 patients relevant to the use of corticosteroids have been published or released (Table 3). The most widely discussed are listed first in the table.[9,10]

SUMMARY

In case series from the COVID-19 outbreak in China, steroid use was common, particularly in patients with severe disease. Steroids were used concomitantly with many other medications, particularly antivirals and antibiotics. Because of the design of these studies, it is not possible to determine whether steroids prevent deterioration or the development of ARDS, or whether they can reduce mortality in ARDS. No study has investigated whether adverse effects of glucocorticoids, particularly hyperglycemia, affects the outcomes of treatment. Nevertheless, the studies support additional investigation of whether steroids have a role in treating serious COVID-19 illness. At least one randomized trial is underway (NCT04273321; Efficacy and Safety of Corticosteroids in COVID-19). Additional case series are unlikely to provide strong evidence either for or against the use of steroids, because it is impossible to separate the effect of steroids from those of concomitant treatments and selection bias.

Wang 2020[9]

Design: Single-center, retrospective series of 46 hospitalized COVID-19 patients (Union Hospital of Huazhong University)

Patients: 46 patients with COVID-19 and high inflammatory markers (3 died)

Treatment: 26 patients received low-dose methylprednisolone (estimated dose was 1-2 mg/kd/d IV for 5-7 days). The authors imply that treatment was "early," although this is not reported clearly.

Results: Average number of days for body temperature to return to the normal range was shorter (2.06±0.28 vs 5.29±0.70) and SpO2 improved faster (8.2 days [IQR 7.0-10.3] vs 13.5 days (IQR 10.3-16); P<.001) on methylprednisolone. There were 2 deaths in the steroid group and 1 death in the non-steroid group. The authors also state, regarding Chest CT on day 7 and 14, that "the absorption degree of the focus was significantly better in patients with administration of methylprednisolone."

Major Weaknesses

- The study reported that 4 outcomes were improved (temperature, SpO2, length of time using supplemental oxygen, and Chest CT), but steroid treatment did not affect inflammatory markers, raising a question of consistency of findings. Other outcomes, such as clinical deterioration, ICU length of stay, or time to full recovery, are not reported.
- There were no consistent criteria for giving or not giving steroids. The authors argue that the patients were similar at baseline; if this were true, then unmeasured, unreported factors influenced treatment, making the study less valid.
- It is likely there were important baseline differences. The authors assert that patients who received or did not receive steroids were similar, but review of the tables and charts suggest that the treatment group on average had higher respiratory rates (28(21,36) vs 24(20,30), P=.039), lower initial temperature (37.6 vs 38.2), and higher SpO2%.

  Inspection of the graphs suggests that patients with lower temperatures were more likely to get methylprednisolone, while those with higher temperatures were less likely to. (Table 1) (This could be related to caution in using steroids in more febrile patients).

Table 1. Treatment with steroids by initial temperature in Wang 2020

	With methylprednisolone	Without methylprednisolone
Temp ≤ 38 degrees	9	1
Temp > 38 degrees	6	10

Bottom Line

Given the biased allocation of treatment, the meaning of the main results—fever and SpO2—is unclear. The study also does not provide valid information about the overall benefits and harms of steroids in COVID-19 pneumonia without ARDS.

Wu 2020[10]

This study attempted to describe risk factors for developing or dying of ARDS in hospitalized patients with COVID-19 pneumonia. Among several factors, steroid use was called out as associated with better outcomes.

Design: Single-center, retrospective series of 201 hospitalized COVID-19 patients (Wuhan Jinyintan Hospital in China).

Patients: Of 201 patients, 84 developed ARDS and 44/84 died.

Treatment: Use of steroids (methylprednisolone) occurred in the environment of other medication use—85% received antivirals, and nearly 100% received antibacterial drugs, regardless of the severity at the time of presentation. Among patients who developed ARDS, 50/84 received methylprednisolone. The dosage, timing, and the criteria for starting a steroid were not clear.

Results: Many patient characteristics were associated with the development of ARDS and death from ARDS. Older age, higher fever, male gender, productive cough, diabetes, and other factors were associated with developing ARDS. Patients who developed ARDS were less likely to receive antiviral therapy that those who did not have ARDS.

The association of steroid use with development of ARDS suggests that steroids were usually started after ARDS developed, as might be consistent with guidelines. Among patients with ARDS, administration of methylprednisolone was associated with a lower risk of dying (HR, 0.38; 95% CI, 0.20-0.72). Among those who received methylprednisolone treatment, 23 of 50 (46.0%) patients died, while of those who did not receive methylprednisolone treatment, 21 of 34 (61.8%) died. The authors interpreted this as evidence of a benefit from steroids.

Major Weaknesses

A major weakness is that there is no information about the baseline characteristics of patients who received methylprednisolone versus those who did not. It is impossible to determine whether patients with ARDS who received methylprednisolone had more severity or comorbidity to begin with.

Bottom Line

This study provides some useful information about risk factors for ARDS and for death in patients with ARDS, but provides very low quality evidence about the effectiveness of steroids in improving survival in patients who develop ARDS.

Sun, 2020[11]

Sun et al conducted a similar study in a series of 165 patients in a Wuhan hospital. Through the end of the follow-up period, 11.5% of patients died, and 61% had been discharged. This study focused on the use of 9 classes of medication in relation to disease progression. This study provides useful information about how various drugs were used, and what combinations of drugs were used, as well as when they were started. Steroids were used in 88.5% of “severe” patients and 64.7% of “non-severe” cases. Forty-five of 139 non-severe cases progressed (became sicker). Of these forty-five, 36 (80%) were taking a steroid; among 94 patients who did not progress, 54 (57%) took a steroid. The main finding of the study was that some drug classes, notably antivirals, were associated with better outcomes when given within 72 hours of admission. Steroids were rarely started within the first 4 days of hospitalization, so the study was not able to determine whether early use of steroids was beneficial.

Liu 2020[12]

Another retrospective, single-center series of 109 COVID-19 cases from Wuhan examined the characteristics of 53 patients who developed ARDS versus 59 who did not. As in other series, steroids were likely to be used in patients once they had developed ARDS. Unlike other series, corticosteroid use had no effect on mortality in the patients with ARDS.

Table 2. Current Guidance

Source	Recommendation	Date Published	Date Accessed
World Health Organization[1] "Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected."	Do not routinely give systemic corticosteroids for treatment of viral pneumonia outside of clinical trials	03-13-2020	03-25-2020
Centers for Disease Control and Prevention[2] "Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)	Corticosteroids should be avoided, because of the potential for prolonging viral replication as observed in MERS-CoV patients, unless indicated for other reasons (*ie*, chronic obstructive pulmonary disease exacerbation, septic shock)	03-07-2020	03-25-2020
American Thoracic Society/Infectious Diseases Society of America[13] "Diagnosis and Treatment of Adults with Community-acquired Pneumonia"	Recommended not to use. May be considered in patients with refractory septic shock	10-01-2019	03-25-2020
Society of Critical Care Medicine[14] "Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)"	For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy ("shock-reversal") over no corticosteroid. In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we suggest against the routine use of systemic corticosteroids. In mechanically ventilated adults with COVID-19 and ARDS, we suggest using systemic corticosteroids over not using corticosteroids	03-20-2020	03-25-2020
U.S. Department of Defense[15] "DoD COVID-19 Practice Management Guide"	Avoid routine steroids in patients without acute respiratory distress syndrome (ARDS) except under certain circumstances. However, consider methylprednisolone for intubated patients with ARDS.	03-23-2020	03-25-2020

Table 3. Published/released studies of COVID-19 patients relevant to the use of corticosteroids

Author/ Year	Location/setting (*ie*, hospital, country)	Dates	Number of cases	Patient characteristics (*ie*, age, gender)	Outcomes Assessed
Wang 2020[9]	Isolation ward of Wuhan Union Hospital in Wuhan, China	• January 20 - February 25, 2020	n=46	• Pneumonia, not ARDS • Age (mean): 54 • Gender (% male): 57% • Comorbidities: - Hypertension (30.8%) - Diabetes (8.7%) - Cardiovascular disease (13%) - Chronic pulmonary disease (6.5%) - Cerebrovascular disease (4.3%) • Cancer (4.3%)	• Days until normal body temperature • Improvement in SpO2 (interval until off supplemental oxygen)
Wu 2020[10]	Wuhan Jinytintan Hospital, China	• December 25, 2019 – January 26, 2020 • Final follow-up date: February 13, 2020	n=201	• Relatively severe COVID-19 pneumonia • Age (median): 51 • Gender (% male): 63.7% • Developed ARDS: 41.8%	• Development of ARDS • Death among ARDS patients
Sun 2020[11]	Zhongnan Hospital of Wuhan University in Wuhan, China	• December 19, 2020 – February 2, 2020 • Final follow-up date: February 12, 2020	n=165 (26 severe cases)	• 84% “non-severe” and 16% “severe” COVID illness • Age (median): 55 • Gender (% male): 50.9% • Comorbidities: - Hypertension (24.8%) - Cardiovascular disease (9.7%) - Diabetes (7.3%) - Cancer (4.8%)	• Disease progression
Liu 2020[12]	Central Hospital of Wuhan (Wuhan, China)	• January 2, 2020 – February 1, 2020	n=109	• Age (mean): 55 • Gender (% male): 54.1% • Developed ARDS: 48.6%	• ARDS

REFERENCES

1. WHO. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. 2020.
2. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). 2020; https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed March 25, 2020.
3. Medicine SoCC. Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). 2020.
4. Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. Cochrane Database Syst Rev. 2019;7:Cd004477.
5. Lian XJ, Huang DZ, Cao YS, et al. Reevaluating the Role of Corticosteroids in Septic Shock: An Updated Meta-Analysis of Randomized Controlled Trials. *Biomed Res Int*. 2019;2019:3175047.
6. Lansbury L, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2019;2:CD010406.
7. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276.
8. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020 Feb 6:S0140-6736(0120)30305-30306.
9. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv. 2020.
10. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;13:13.
11. Sun F, Kou H, Wang S, Lu Y, Zhao H, Li W. Medication Patterns and Disease Progression Among 165 Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: A Single-Centered, Retrospective, Observational Study. *Lancet*. 2020.
12. Liu YH, Sun W, Li J, et al. Clinical features and progression of acute respiratory 1 distress syndrome in oronavirus disease 2019. MedRxiv. 2020.
13. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e47.
14. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). 2020.
15. DoD. DoD COVID-19 Clinical Practice Management Guide. 2020.

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