Corticosteroid Therapy for COVID-19 Infection

QUESTIONS

1. In hospitalized patients who have COVID-19 infection, what are the benefits and harms of corticosteroids?
2. Do these benefits and harms vary by patient characteristics, disease severity, or specific medication, dose, or timing?

RATIONALE

Acute respiratory distress syndrome (ARDS) from COVID-19 has a high mortality rate and is associated with a hyperinflammatory state characterized by fulminant multi-organ failure and elevated cytokine levels. Given that corticosteroids have been used for decades in treatment of pneumonia, ARDS, and sepsis – albeit with mixed results – clinicians and researchers have hypothesized that steroids might be beneficial in some patients who have COVID-19 disease if treatment is timed correctly.

Early studies of steroids for COVID-19 were observational and had serious methodological flaws and conflicting results.

However, during the week of June 22, 2020, a preliminary, not yet peer-reviewed report of the "RECOVERY" trial[1] indicated that dexamethasone treatment (6 mg IV or PO for up to 10 days) reduced 28-day mortality and hospital length of stay compared with usual care. RECOVERY is a large, randomized, adaptive trial in the UK comparing several treatments for patients hospitalized with COVID-19. In prespecified subgroup analyses the effects of dexamethasone appear to be most beneficial in: 1) hospitalized adults receiving invasive mechanical ventilation or oxygen supplementation; 2) men; 3) patients < 70 years of age; and 4) those with a symptom duration of > 7 days.

We have updated our report to incorporate the preliminary findings from this study.

BACKGROUND

Review of the literature about steroids in pneumonia, ARDS, and sepsis lends some credibility to the hypothesis that, if timed correctly and used in an appropriate target population, steroids might be beneficial in some patients.

Steroid therapy is commonly used in the critical care setting for patients with community-acquired pneumonia, ARDS, or sepsis. Treatment with steroids is not controversial in patients with CAP or ARDS complicated by reactive airway disease, either existing before or developing as a result of the acute illness. For other patients, the literature on steroids is puzzling because there is large variation in results even among well-conducted studies, with some indicating large reductions in mortality, length of stay, and ventilator days, and others indicating no or small effects.

Pneumonia: In a well-conducted 2015 meta-analysis, steroids (equivalent of prednisone 0.5 mg/kg) reduced mortality in patients with severe community-acquired pneumonia (CAP), but not in CAP patients overall.[2] The large VA Cooperative Trial ESCAPE[3] of 7 days of methylprednisolone (bolus followed by 40/mg day for 7 days) is not yet reported. In the other large trial[4] IV dexamethasone 5 mg/d in CAP reduced median length of stay by 1 day (6.5 vs 7.5 days) but did not reduce mortality. As in other trials, hyperglycemia was common (44% vs 23%).[5]

ARDS: The Society for Critical Care Medicine, using updated Cochrane reviews on ARDS[6] and of influenza,[7] found that, in patients with ARDs, steroids reduced mortality and length of stay. Recently, a multicenter trial in 277 patients from MICUs in Spain found that dexamethasone 20 mg once daily from day 1 to day 5, then 10 mg once daily from day 6 to day 10, reduced ventilator days and 28-day mortality compared with continued usual care in patients with moderate-severe ARDS.[8] 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.

Sepsis: A systematic review of septic shock patients (not with COVID-19) indicating that low-dose steroids reduced ICU length of stay,[9] 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. By including a longer follow-up period, the large, recent, well-conducted ADRENAL trial provided important lessons for studying the use of steroids in very ill patients. A total of 3,800 participants with septic shock received a continuous IV infusion of hydrocortisone at a dose of 200 mg daily for 7 days or a placebo. Patients who had been assigned to receive

hydrocortisone had faster resolution of shock than did those assigned to the placebo group, but there was no difference in ventilator-free days of life or overall 90-day mortality.[10,11] The trial elegantly demonstrated the hazards of focusing on short-term outcomes in the initial episode of illness.

In summary, while it is difficult to draw firm conclusions, careful analysis of the relationship between clinical characteristics, timing of treatment, and results in the major trials and meta-analyses suggests that adjunctive corticosteroids are most likely to be beneficial in ARDS, CAP, and shock patients with high inflammatory biomarker indices or recent clinical deterioration. This conceptual model underlies the approach taken in the RECOVERY trial; as the investigators put it:

> "It is likely that the beneficial effect of corticosteroids in severe viral respiratory infections is dependent on using the right dose, at the right time, in the right patient. High doses may be more harmful than helpful, as may corticosteroid treatment given at a time when control of viral replication is paramount and inflammation is minimal."

LIVING REVIEW METHODS

This living, rapid review was first released in April, 2020 and is being regularly updated, with searches of MEDLINE, EMBASE, and medRxiv completed on a weekly basis. The most recent search was completed on June 23, 2020, with new evidence from case series and the UK RECOVERY trial being added. For the UK Recovery trial and some other studies, we used study protocols and entries in clinical trial registries

Study, population, disease severity, and intervention characteristics were extracted by 1 individual and verified by a second. Two of the investigators applied the Cochrane Risk of Bias tool to assess study risk of bias for randomized trials. Assessment of study limitations in case series was done without the use of a standard instrument. We assessed overall certainty of evidence for critical outcomes: mortality, clinical improvement, hospital length of stay, and harms using criteria based on GRADE.

KEY FINDINGS

- In a large, multicenter, randomized, open label trial conducted in the UK (the RECOVERY trial), dexamethasone 6 mg IV or PO (median treatment duration = 6 [IQR: 3-10 days]) reduced age-adjusted 28-day mortality in hospitalized COVID-19 patients by 17% (21.6% vs 24.6%, RR 0.83; 95%CI 0.74 to 0.92; P<0.001).
    - The mortality reduction was greatest (29.0% vs 40.7%, RR 0.65 [95%CI 0.51 to 0.82]; p<0.001) for adult patients receiving invasive mechanical ventilation (mechanical ventilation or ECMO).
    - In hospitalized patients who received supplemental oxygen without invasive mechanical ventilation, mortality was reduced by about 20% (21.5% vs 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002).
    - Dexamethasone did not reduce mortality in patients not receiving oxygen supplementation (17.0% vs 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14). This result represents a concerning signal for potential harm.
    - The effect of dexamethasone varied by age, sex, and symptom duration but not baseline risk of 28-day mortality. Dexamethasone's effectiveness may be limited to men, individuals age <70 years, and those having symptoms > 7 days prior to treatment.
- The RECOVERY trial is a well-designed, well-conducted trial. The benefit that was observed is likely due to the effect of dexamethasone and not to problems with the design or conduct of the trial.
- Taking all the limitations of the study into account, the relative effect is very likely to be valid and the benefits overall outweigh the harms of treatment. A large, simple trial like RECOVERY provides stronger evidence than a meta-analysis of several small ones.
- However, the overall strength of evidence for the use of dexamethasone is moderate rather than strong because there is only 1 trial, and it has limitations. Specifically,

    (1) The benefit may not be as large in other populations and settings, as it represents one population in one setting at one particular phase of the epidemic.

(2) The report and findings are preliminary – for example, no adverse event data were reported, and some of data from the electronic medical record has not yet been collected. Experience with other critical illness suggests that the 28-day results should be verified with longer follow-up.

(3) Information about comorbid conditions or factors, such as dose response or inflammatory response, that could strengthen causal inference, is lacking.

(4) It is unclear if the following individuals who require oxygen supplementation benefit from dexamethasone: women, individuals older than age 70, and those having symptom duration ≤7 days

- Implementing the results is difficult because criteria for hospitalization, starting or continuing mechanical ventilation, and "requiring oxygen" vary. For example,
    - In light of the suggestion of possible harm in patients who did not require oxygen, less strict criteria for administering supplemental oxygen could mean that patients who were in the group (including women, those older than age 70, or those with symptoms ≤7 days) that did not benefit or were possibly harmed in 1 setting are strong candidates for treatment in another setting.
    - The trial doesn't provide any evidence about benefit or harm for patients over 80 years, and current evidence suggest no benefit for those 70 years of age and older. There is also no information on patient race/ethnicity, and it is likely that few racial minorities especially relevant to the US (*eg*, Blacks, Hispanics, Native Americans) were enrolled. Clinicians might have considered very elderly or more frail patients unsuitable for mechanical ventilation, ICU, hospitalization (vs hospice), or randomization, but these patients would be "eligible" for treatment in the US..
- Because dexamethasone has no mineralocorticoid activity, the results of RECOVERY should not be generalized to other corticosteroids.
- To date, observational studies do not contribute to the overall strength of evidence.

SUMMARY OF EVIDENCE

The RECOVERY Trial (see Table 1 below)[1]

Design: RECOVERY is a large, ongoing, multicenter, randomized, controlled, open-label, adaptive trial conducted in 176 UK National Health Service hospitals. It is designed to compare several treatments and to start and stop treatment arms based on interim data analysis. (For example, the RECOVERY hydroxychloroquine arm was stopped because of lack of efficacy.) This was a large, simple or "pragmatic" trial that was deliberately flexible in the trial protocol and that collected minimal data to facilitate rapid enrollment and reporting of results.

Treatment: One treatment arm was dexamethasone 6mg orally or intravenously once daily for up to 10 days (median = 6 days [IQR 3-10 days]) or until hospital discharge or death. Usual care, according to the local hospital and attending physician, was the comparison group.

Eligibility: Patients were eligible if they were hospitalized with clinically suspected or laboratory-confirmed SARS-CoV-2 infection and had no medical history that might, in the opinion of the attending physician, put the patient at significant risk if (s)he were to participate. The attending physician could exclude a patient who should have definitely received any of the study drugs or who had a contra-indication to any of the study drugs.

Outcomes and Analyses: The primary outcome was 28-day mortality. Secondary outcomes included hospital length of stay and a combined outcome that included death and progression to invasive mechanical ventilation. Pre-specified analyses of the primary outcome were performed in 5 subgroups defined by characteristics at randomization: age, sex, level of respiratory support, days since symptom onset, and predicted 28-day mortality risk.

Patients: A total of 6425 hospitalized patients (2104 allocated to dexamethasone and 4321 to usual care) with confirmed or suspected COVID-19. Pregnant or breast-feeding women were eligible (but received hydrocortisone instead of dexamethasone). The mean age was 66 years (66.9 years in those allocated to dexamethasone and 65.8 years in those receiving usual care) and 36% were female. SARS-CoV-2 infection was confirmed in 82%. The mean symptom duration was approximately 9 days. At randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only, and 24% were receiving neither (typically oxygen saturation >94% on room air). Patients receiving supplemental oxygen at

randomization were older, had a longer symptom duration, were more likely to be male, and to have a confirmed positive SARS-Cov-2 test result than patients not receiving oxygen supplementation.

Main Results: Preliminary results indicate that overall, dexamethasone reduced age-adjusted mortality within 28 days compared with usual care. Based on prespecified subgroup analyses, the relative and absolute effect may have varied by baseline oxygen supplementation requirements, patient age, sex, and symptom duration (test for trend P<0.001). Overall dexamethasone reduced age-adjusted mortality by 17% (21.6% vs 24.6%, RR 0.83; 95%CI 0.74 to 0.92; P<0.001). Among adults receiving invasive mechanical ventilation dexamethasone reduced deaths by about one-third ((29.0% vs 40.7%, RR 0.65 [95%CI 0.51 to 0.82]; p<0.001) and by about one-fifth in adults receiving oxygen without invasive mechanical ventilation (21.5% vs 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002). Dexamethasone did not reduce mortality in patients not receiving oxygen supplementation (17.0% vs 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14). The effect on mortality did not appear to differ by baseline 28-day predicted mortality risk categories.

Additional Analysis: In additional prespecified analyses, the effects of dexamethasone may have been limited to adults age < 70, men, and those with symptoms at least 7 days in duration. Allocation to dexamethasone was also associated with a shorter hospitalization duration and a reduced risk of progression to invasive mechanical ventilation. Effectiveness of dexamethasone on hospitalization and progression to invasive ventilation may have been limited to individuals receiving oxygen supplementation at baseline. Harms data and the proportion of patients receiving IV versus PO dexamethasone were not reported.

Risk of Bias Assessment: Based on the information provided to date, the risk of bias was low. Randomization appears successful in assembling comparable groups. Loss to follow-up was low and methods for handling missing data were appropriate. A total of 7% of the usual care group got steroids. The study was not blinded and deviations from the study protocol were permitted. This approach facilitates recruitment, collection of the main measures, and reporting of results, but sacrifices detailed information linking the treatment to some patient characteristics and details of the treatment, such as how many doses were given and whether that was related to the outcomes. Unblinded physicians can influence 28-day mortality as well as the timing of initiation or withdrawal of mechanical ventilation; longer follow-up would address this concern.

Effects of Mortality Rate and Practice Patterns on Target Population: The mortality rate in the usual care group was 28%. Differences in practice patterns as well as the particular stage of the epidemic might account for this mortality rate. Assuming relative effects translate to groups with lower mortality rates, the absolute effect would be smaller, and the number needed to treat to see a benefit would be larger.

Differences in practice patterns make it difficult to apply the study results in other settings, including the US. Using “requiring oxygen” as a criterion for treatment is the biggest concern. If criteria for use of supplemental oxygen were stricter in the UK— for example, if fewer patients with an O2 of 87 to 90% get oxygen—then we would be treating patients who might be on the wrong side of the nebulous cutoff between “requiring oxygen” (benefit) and “not requiring oxygen” (possible harm). Policies about whom to admit to the hospital, which patients should be put on mechanical ventilation, and how long to continue intensive care when the patient is worsening or not improving all affect the target population. Differences in these clinical factors can change the size of the benefit but are unlikely to change the direction of the effect.

Observational Studies

Observational studies of corticosteroids in COVID-19 patients had mixed results and serious methodological flaws. See the Appendix for a detailed discussion of these studies.

While small case series are unlikely to provide useful information, larger, well-designed, prospective observational studies could help determine whether the results observed in the RECOVERY trial are applicable in US and other settings, and further refine which patients are likely to benefit.

CURRENT GUIDANCE

Treatment with steroids is not controversial in patients with CAP or ARDS complicated by reactive airway disease, either existing before or developing as a result of the acute illness. Guidelines focus on patients who do not have another indication for steroid treatment.

In general, Chinese guidelines recommended wide use of low-dose glucocorticoids, accounting for the high rates of steroid use in the case series from Wuhan described in the Appendix.

Prior to the RECOVERY trial, SCCM/Surviving Sepsis suggest using corticosteroids in the sickest mechanically ventilated adults with COVID-19 and ARDS. This was a “weak” recommendation—some panelists disagreed and the evidence is not strong.[3] NIH guidelines provided a “moderate” recommendation for using low-dose corticosteroid therapy (*ie*, shock reversal) over no corticosteroids for adults with COVID-19 and refractory shock. The NIH stated that there is insufficient evidence to recommend for or against the use of systemic corticosteroids in mechanically ventilated patients with ARDS.

The NIH is revising its guidance regarding dexamethasone use in COVID-19 patients on mechanical ventilation and in hospitalized COVID-19 patients who require supplemental oxygen. Check their web site for news of revisions.[12] All the other organizations are updating their guideline because of the RECOVERY trial results.

Table 1. Horby et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report. RECOVERY Collaborative Group. June 22, 2020.[1]

Location/ setting (*ie*, hospital, country, dates	Number of participants	Patient characteristics (*ie*, age, gender)	Treatment allocation		Study outcomes	Study results		RR (95% CI), p-value
			Dex treatment	Usual care		Dex treatment	Usual care	
176 National Health Service (NHS) hospitals in the UK; inpatient wards and ICU; March 19 – June 8, 2020	n=6425 n=2104 (dex treatment) n=4321 (usual care)	Age (mean) < 70 >= 70 to < 80 >= 80 Gender (% male): Days since symptom onset Respiratory support received No oxygen received Oxygen only Invasive mechanical ventilation (MV) or ECMO Comorbidities: Diabetes Heart disease Chronic lung disease Tuberculosis HIV Severe liver disease Severe kidney impairment Any of the above SARS-CoV-2 test result Positive Negative Unknown	66.9 (15.4) 1142 (54%) 467 (22%) 495 (24%) 1338 (64%) 8 (5-13) 501 (24%) 1279 (61%) 324 (15%) 521 (25%) 586 (28%) 415 (20%) 6 (< 0.5%) 12 (1%) 37 (2%) 167 (8%) 1174 (56%) 1702 (81%) 213 (10%) 189 (9%)	65.8 (15.8) 2506 (58%) 860 (20%) 955 (22%) 2750 (64%) 9 (5-13) 1034 (24%) 2604 (60%) 683 (16%) 1025 (24%) 1171 (27%) 931 (22%) 19 (< 0.5%) 20 (< 0.5%) 82 (2%) 358 (8%) 2417 (56%) 3553 (82%) 397 (9%) 371 (9%)	**Primary outcome:** 28-day mortality **Secondary outcomes:** Discharged in 28 days Receipt of MV or death** MV** Death**	454 (21.6%) 1360 (64.6%) 425/1780 (23.9%) 92/1780 (5.2%) 360/1780 (20.2%)	1065 (24.6%) 2639 (61.1%) 939/3638 (25.8%) 258/3638 (7.1%) 787/3638 (21.6%)	0.83 (0.74-0.92) < 0.001* 1.11 (1.04-1.19) 0.002 0.91 (0.82-1.00) 0.049 0.76 (0.61-.096) 0.021 0.91 (0.82-1.01) 0.07

Dex = dexamethasone

*Results may have varied by respiratory support received, age, sex and symptom duration with effect possibly limited to those receiving oxygen supplementation or invasive mechanical ventilation, men, those age <70 years and individuals having symptom duration >7 days.

**Analyses excludes patients on invasive mechanical ventilation at randomization

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APPENDIX: SUMMARY OF OBSERVATIONAL STUDIES

Results from case series (see Appendix Table)

- Eight studies from the COVID-19 outbreak are included in this living review.[13-20] Six case series were from China, 1 was from Spain,[20] and 1 was from the US.[19] Severity of COVID-19 disease and the outcomes assessed varied across studies. All studies used corticosteroids with both glucocorticoid and mineralocorticoid effects. In general, patients had ARDS, but the criteria for using corticosteroids was often not well-defined.
- 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.
- Baseline differences between groups receiving corticosteroids versus no corticosteroids limit the conclusions that can be made about the effectiveness of treatment. Another significant limitation in many of these studies are a lack of reported treatment protocols and defined criteria for treating patients with corticosteroids.
- 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.

A study from the US describes the impact of a protocol for corticosteroid use in patients hospitalized for COVID-19 pneumonia in 5 hospitals within 1 hospital system.[19] Instituting the protocol increased the proportion of patients who were given steroids early in their hospitalization. The authors concluded that an early short course of methylprednisolone in patients with moderate to severe COVID-19 pneumonia reduced a composite endpoint of death, transfer to intensive care, and need for mechanical ventilation (34.9% vs 54.3%, p=0.005). One series from China[9] also reported that, among 84 patients with ARDS, administration of methylprednisolone was associated with a lower risk of dying. However, it is impossible to determine whether patients with ARDS who received methylprednisolone had more severity or comorbidity to begin with.

One Spanish study[8] adjusted for baseline differences using a propensity score and reported that in-hospital mortality was lower in patients treated with steroids than in controls (13.9% vs 23.9%, OR 0.51 [0.27-0.96], p= 0.044). In-hospital mortality was not different between initial regimens of 1 mg/kg/day of methylprednisolone and steroid pulses.

Unlike the findings of Wang[10] who reported reduced length of ICU hospitalization and length of hospitalization with methylprednisolone, there were no differences in duration of symptoms and length of hospital stay between those who received corticosteroid treatment and those who did not in a series of COVID-19 cases.[11] However, the series by Zha[11] included patients with mostly mild disease and no patients developed ARDS or died.

In 1 non-peer reviewed study, 80% of 45 “non-severe” patients whose disease progressed were taking a steroid.[12] In another retrospective study,[13] steroids were likely to be used in patients once they had developed ARDS. Unlike the series by Wu[9] and Fernandez Cruz,[8] corticosteroid use had no effect on mortality in the patients with ARDS 13. Seven out of 15 patients with COVID-19 and ARDS died in a series where all patients received corticosteroid treatment along with antibiotic and/or antiviral co-treatments.[14]

Further details about the included studies can be found in the Appendix Table.

SUMMARIES OF INDIVIDUAL CASE SERIES

Fadel 2020[19]

Design: Single pre-test, single post-test study. Consecutive eligible patients admitted after a corticosteroid protocol was implemented (after March 20, 2020) were compared to those admitted before the protocol was implemented (March 12, 2020 through March 19, 2020). To mitigate the biases inherent in an observational study, the investigators used a multivariate logistic regression, a nonequivalent dependent variable analysis, and a sensitivity analysis.

Patients: A total of 213 patients who required oxygen by nasal cannula, high flow nasal cannula, or mechanical ventilation, had radiographic evidence of bilateral pulmonary infiltrates, and were hospitalized for at least 24 hours were included.

Treatment: "Standard of Care" versus "Early CP" (care delivered after a protocol for an early, short course of corticosteroids was implemented)

Results: Primary outcome: a composite of escalation to intensive care from a general medical unit, progression to respiratory failure requiring mechanical ventilation after hospital admission, or in-hospital mortality. Secondary outcomes: Development and severity of ARDS, days to ventilator liberation, shock, acute kidney injury, and length of hospital stay.

Fadel Results

Outcome frequency (unadjusted)	SOC	CP	Odds Ratio
Transfer to MICU, n (%)	31 (44%)	32 (27.3%)	0.47 (0.25-0.88)
Escalation to mechanical ventilation, n (%)	26 (36.6%)	26 (21.7%)	0.47 (0.25-0.92)
Mortality, n (%)	21 (26.3%)	18 (13.6%)	0.45 (0.22-0.91)
Development of ARDS (%)	31 (38.3%)	33 (26.6%)	*
Length of Stay (IQR) - days	8 (5-14)	5 (3-7)	**

* p=0.04
**p<0.001

Bottom line

Despite some strengths, this study is inadequately controlled and provides little evidence to support the use of corticosteroids in hypoxic or deteriorating hospitalized COVID-19 patients with pneumonia. Randomized trials underway now should provide reliable findings on this question.

In this study, patients treated after March 20, 2020 were compared to those treated March 12, 2020 through March 19, 2020. Many other changes in management were instituted before and during use of the steroid protocol, making the use of historical controls hazardous. The analyses undertaken to mitigate bias were not effective in this situation.

Centers that have not adopted a corticosteroids protocol have also observed less need for MICU transfers and mechanical ventilation with the first month after a surge.

Wang 2020[14]

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." Update – additional outcomes from published article https://www.nature.com/articles/s41392-020-0158-2#MOESM1: 3 out of 20 (11.5%) patients on methylprednisolone received mechanical ventilation vs 7 out of 20 (35%) without methylprednisolone (p=0.05). Additionally, the length of ICU hospitalization was significantly shorter in patients with methylprednisolone

treatment (8 days [IQR 6–9] vs 15 days [IQR 9–19]; P < 0.001) and length of hospitalization (14 days [IQR 11–16] vs 22 days [IQR 18–26]; P < 0.001,

Major Weaknesses

- The study reported that outcomes were improved (temperature, SpO2, length of time using supplemental oxygen, ICU length of stay and Chest CT), but steroid treatment did not affect inflammatory markers, raising a question of consistency of findings. (NB: Outcome of temperature is reported in pre-print but not in the published version of the article)
- 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. Both groups received additional treatment such as antiviral therapy and antibiotics; however, there is no mention of differences in other medications between the 2 groups.
- 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 in the pre-print version of the study suggests that patients with lower temperatures were more likely to get methylprednisolone, while those with higher temperatures were less likely to. (This could be related to caution in using steroids in more febrile patients).

Treatment with Steroids by Initial Temperature in Wang 2020 (pre-print version)

	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[15]

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.

Sun, 2020[13]

Sun et al conducted 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[18]

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.

Zha 2020[16]

A retrospective series of 31 COVID-19 patients from Wuhu, China (500km from Wuhan). None of the patients developed ARDS and no patients died. Eleven out of 31 patients received treatment with corticosteroid (40 mg methylprednisolone once or twice per day) within 24 hours of admission for a median 5 days (IQR, 4.5–5.0 days). Patients given corticosteroid treatment had higher temperature on admission, had higher median CRP levels, lower median lymphocyte count, and more abnormalities on chest CT. There were no differences in time to virus clearance, duration of symptoms, and length of hospital stay between those who received corticosteroid treatment and those who did not.

Zhou 2020[17]

A retrospective case series of 15 COVID-19 patients from Wuhan, China. All patients showed bilateral pneumonia, hypoxemia and moderate or severe ARDS, 14 (93%) had infections, 8 (53%) accompanied by shock, and 9 (60%) with multiple organ injuries. All patients had received treatments containing noninvasive oxygen therapy and antibiotics and/or antiviral agents before and after ICU admission, and hypoxemia was not improved by these treatments. Corticosteroids (median hydrocortisone-equivalent dose of 400.0 mg/day) initiated immediately after ICU admission for an average of 9.5 days. Seven out of the 15 (46.7%) patients died. The small sample size and lack of control group limit any conclusions that can be made about the benefits and harms of corticosteroid therapy from this study.

Fernandez Cruz 2020[20]

A retrospective analysis where patients treated with corticosteroids (n=396) were compared to patients not treated with corticosteroids (n=67). Baseline differences were adjusted for by a propensity score, which predicts the patient's probability of being treated with steroids regardless of confounding factors, using multivariable logistic regression. Treatment with corticosteroids and other treatments were at the discretion of the physician rather than according to a clear protocol or patient criteria. Corticosteroid treatment was given a median of 10 days after symptom onset. Over 90% of patients also received hydroxychloroquine. In-hospital mortality was lower in

patients treated with steroids than in controls (13.9% vs 23.9%, OR 0.51 [0.27-0.96], p= 0.044). Steroid treatment reduced mortality by 41.8% relative to no steroid treatment (RRR 0.42 [0.048 to 0. 65]). The authors calculated a NNT (number necessary to treat) of 10. The difference in mortality persisted after applying the propensity score adjusted for steroid treatment. In-hospital mortality was not different between initial regimens of 1 mg/kg/day of methylprednisolone and steroid pulses.

Appendix Table. 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[14]	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 (pre-print version only) • Improvement in SpO2 (interval until off supplemental oxygen) • Number on mechanical ventilation • Length of ICU stay and length of hospitalization
Wu 2020[15]	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[13]	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[18]	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
Zha 2020[16]	Second People's Hospital of Wuhu and Yijishan Hospital, Wuhu, China	• January 24, 2020 – February 24, 2020	n=31	• Pneumonia: 94% (not ARDS) • Age (median): 39 (IQR, 32-54) • Gender (% male): 64% • Comorbidities: - Hypertension (23%) - Cardiovascular disease (3%) - Diabetes (3%) - Chronic Hep B (6%)	• Time to virus clearance • Clinical recovery • Length of hospital stay

Zhou 2020[17]	Wuhan Pulmonary Hospital	• January 1, 2020 – January 29, 2020	n=15	• ARDS • Infections: 93%; Shock: 53%; multiple organ injury: 60% • Age (mean): 62 • Gender (% male): 67% • Comorbidities: - Hypertension (40%) - Diabetes (47%) - Heart disease (27%)	• Mortality • Oxygen saturation (SaO_2) • White blood count
Fernandez Cruz 2020[20]	Hospital Puerta de Hierro-Majadahonda, Madrid, Spain	• March 4, 2020 – April 07, 2020	n=463	• Pneumonia (64% ARDS) • Gender (% male): 68% • Age (mean): 67 • Comorbidities: - Hypertension (46%) - Diabetes (20%) - Heart disease (18%)	• In-hospital mortality
Fadel 2020[19]	Henry Ford Hospital System, Detroit, Michigan, USA	• March 12, 2020 – March 27, 2020	n=213	• Pneumonia • Gender (% male): 51% • Age (median): 65 • Comorbidities: - Hypertension (74%) - Diabetes (49%) - COPD (13%)	• Primary composite outcome: escalation to ICU, progression to mechanical ventilation after admission, or in-hospital all-cause mortality. • ARDS • Days to ventilator liberation, • Shock, • Acute kidney injury (AKI), • Length of hospital stay