

COVID-19: SYSTEMIC CORTICOSTEROIDS FOR HOSPITALIZED PATIENTS



A Rapid Guidance Summary from the Penn Medicine Center for Evidence-based Practice
 Last updated July 27, 2020. All links rechecked July 27 unless otherwise noted.

This Rapid Guidance Summary is a description of existing guidance and evidence reviews from a variety of sources that was in effect at the time of publication. It should not be used or interpreted as a clinical practice guideline, but instead can be used in development of local recommendations and policies.

Key questions answered in this summary

- How should corticosteroid drugs be used in patients with severe COVID-19 disease?
Management of patients who are taking corticosteroids for chronic conditions, use of inhaled corticosteroids, and treatment of patients who are pregnant is outside the scope of this report.

Summary of major recommendations

- Most recent clinical practice guidelines are now consistently recommending use of dexamethasone for patients with severe COVID-19 disease. Other guidelines are alerting users that guidance may change when the results of the RECOVERY trial are peer-reviewed and published.
- Earlier guidelines recommended against routine use of corticosteroids, but some made weak recommendations for corticosteroids in patients with acute respiratory distress syndrome from severe COVID-19 disease.
- The emerging consensus across professional society and medical center guidance is to use corticosteroids only if the patient condition is severe enough to require supplemental oxygen.
- There is little direct evidence from controlled clinical trials on safety and adverse events of corticosteroids in COVID-19 illness in different subpopulations of patients.

Public health agency and professional society guidelines on corticosteroids

Source	Recommendations
Australia July 23	Consider using dexamethasone 6 mg daily intravenous or oral for up to 10 days in adults with COVID-19 who are receiving oxygen. (interim recommendation awaiting complete reporting). Do not routinely use dexamethasone to treat COVID-19 in adults who do not require oxygen. (interim recommendation awaiting complete reporting)
NIH July 17	The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated (strong recommendation based on RCT evidence) and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (moderate recommendation based on RCT evidence). The Panel recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (strong recommendation based on RCT evidence). See the Panel's guidance on the use of dexamethasone for a detailed discussion of these recommendations. <i>CEP NOTE: the panel recommendations are based on the unpublished preliminary results of the RECOVERY trial.</i> <i>CEP NOTE: additional guidance available for patients on corticosteroids for a chronic condition.</i>

Source	Recommendations
ACP July 16	While full review of the RECOVERY trial dexamethasone results is pending, corticosteroids are otherwise not recommended for routine treatment of less severely ill patients with COVID-19 (not requiring oxygen or ventilation), unless otherwise required (e.g. for treatment of acute exacerbation of COPD). Corticosteroids have the potential to prolong viral replication, based on lessons learned from MERS-CoV.
IDSA June 25	Among hospitalized patients with severe COVID-19, the IDSA guideline panel suggests glucocorticoids rather than no glucocorticoids. (Conditional recommendation, Moderate certainty of evidence) Among hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen [i.e. patients without severe disease], the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)
DoD June 18	The use of glucocorticoids is controversial and the risks must be weighed against the potential benefit. <i>CEP NOTE: The guideline developers make note of the preliminary reports from the RECOVER trial but do not base recommendations on those findings because they have not been peer-reviewed</i>

Recent systematic reviews with quantitative data synthesis

Reviewer	Findings
VA-ESP June 26	<p>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% vs24.6%, RR 0.83; 95%CI 0.74 to 0.92; P<0.001).</p> <p>The mortality reduction was greatest (29.0% vs40.7%, RR 0.65 [95%CI 0.51 to 0.82]; p<0.001) for adult patients receiving invasive mechanical ventilation (mechanical ventilation or ECMO).</p> <p>In hospitalized patients who received supplemental oxygen without invasive mechanical ventilation, mortality was reduced by about 20% (21.5% vs25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002).</p> <p>Dexamethasone did not reduce mortality in patients not receiving oxygen supplementation (17.0% vs13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14). This result represents a concerning signal for potential harm.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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,</p> <ol style="list-style-type: none"> 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 <p>Implementing the results is difficult because criteria for hospitalization, starting or continuing mechanical ventilation, and “requiring oxygen” vary. For example,</p> <p>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 1setting are strong candidates for treatment in another setting.</p>

Reviewer	Findings
	<p>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 (e.g. 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.</p> <p>Because dexamethasone has no mineralocorticoid activity, the results of RECOVERY should not be generalized to other corticosteroids.</p> <p>To date, observational studies do not contribute to the overall strength of evidence.</p>

Systematic reviews with search dates prior to May 15, 2020 and systematic reviews that combined results from studies of COVID-19 patients and patients with other respiratory infections are not included.

Other recent evidence reviews referencing RECOVERY trial data

Reviewer	Findings
BMJ Best Practice July 27	<p>Consider low-dose dexamethasone for the management of hospitalized patients with COVID-19 who require oxygen or ventilation.</p> <p>Dexamethasone is associated with reduced mortality risk in patients with severe COVID-19 according to results (preliminary results from a preprint study, not peer reviewed) from the RECOVERY trial in the UK. (†)</p> <p>As a consequence of this trial, in the UK low-dose dexamethasone is now indicated for the treatment of suspected or confirmed COVID-19 in hospitalized adults receiving oxygen therapy, non-invasive or invasive ventilation, or extracorporeal membrane oxygenation. Oral prednisolone or intravenous hydrocortisone is recommended in pregnant or breastfeeding women. Use in children is still being studied.</p>
ACP July 24	<p>The UK national RECOVERY trial (Randomized Evaluation of COVid-19 tHERapY) is a randomized clinical trial with patients from over 175 British hospitals, with multiple arms testing a range of potential treatments for COVID-19. The low-dose dexamethasone treatment arm randomized 2104 patients to receive dexamethasone 6 mg once per day (by mouth or IV) for ten days and compared outcomes with 4321 patients randomized to usual care alone. Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.64, 95% confidence interval 0.51 to 0.81) and by one fifth in other patients receiving oxygen but not mechanically ventilated (rate ratio 0.82, 95% CI 0.72 to 0.94). There was no benefit among those patients who did not require respiratory support (rate ratio 1.19, 95% CI 0.91 to 1.55).</p>
EM-RAP July 23	<p>Dexamethasone should be considered for patients requiring supplemental oxygen.</p> <p><u>Corticosteroids</u>: Initially, concern for increased viral shedding or reduced viral clearance limited steroid use in COVID-19 to patients with other clinical indications (eg, COPD, asthma, or septic shock).</p> <p>Currently, the best available evidence supports the use of steroids in patients with COVID-19 requiring supplemental oxygen.</p> <p><u>Dexamethasone</u>: There is evidence that dexamethasone decreases time on the ventilator and decreases mortality in moderate to severe ARDS. Dexamethasone has a theoretical benefit over other steroids in ARDS due to decreased mineralocorticoid effect and hence less fluid retention.</p> <p>On June 22nd, 2020 the RECOVERY Collaborative Group from Oxford published a pre-release non-peer reviewed paper on the effect of dexamethasone in hospitalized patients with COVID-19. (†) Patients not requiring supplemental oxygen did not benefit from dexamethasone. In fact, there was a trend towards worse outcomes. In patients receiving supplemental oxygen, 30 patients needed to be treated to prevent one death. In ventilated patients, this number was less than 10. Only 28-day mortality was reported. It is possible that a longer term outcome such as 90-day mortality might not be as positive. This is part of a much larger study with multiple arms; no subsets have been reported to date.</p> <p><u>It is our opinion that current data are robust enough to institute therapy with dexamethasone until further data become available.</u></p> <p><u>Methylprednisolone</u>: There may be a mortality benefit for COVID-19 patients with ARDS who are treated with methylprednisolone. Current evidence should be interpreted with caution: data are from one small study that examined the sickest patients.</p>

Reviewer	Findings
Penn Medicine July 23	<p>Corticosteroids (both inhaled and systemic) have mixed data with some studies suggesting potential improvement in ARDS and others suggesting worse outcomes and prolonged viral shedding. Corticosteroids are recommended in patients with other compelling indications as well as in patients with refractory septic shock when benefits outweigh risks. Corticosteroids can also be considered in patients with ARDS when potential benefits outweigh risks and after discussion with infectious diseases and pulmonary.</p> <p>The Penn Medicine COVID-19 Therapeutics Panel is awaiting availability of full results of the RECOVERY trial and will develop revised guidelines in conjunction with the Penn Medicine Critical Care Collaborative on the use of corticosteroids. (†)</p> <p><i>CEP NOTE: the full review includes summaries of each of the individual studies plus additional information on the limitations of the available evidence.</i></p>
ASHP July 23	<p>Preliminary data analysis of the RECOVERY trial indicates that overall 28-day mortality was reduced in patients receiving dexamethasone compared with those receiving standard care (21.6 vs 24.6%) with the greatest benefit observed in patients requiring mechanical ventilation at enrollment.</p> <p>Data on the use of corticosteroids in COVID-19 are limited. The benefits and risks of corticosteroid therapy should be carefully weighed before use in patients with COVID-19.</p>
Hopkins June 28	<p>The RECOVERY trial provides the first evidence of therapy that provides a mortality benefit to those who are mechanically ventilated (or who require oxygen (severe COVID-19). In this trial, there was a trend toward increased mortality in those who do not require oxygen, so not recommended in this group usually with early infection. (†)</p> <p>Some aspects of the RECOVERY trial deserve comment: the UK trial mortality was unusually high if the same benefit would be witnessed in North America is less clear. Also, patients with less than 7d of symptoms appeared to not benefit, suggesting that the during early phase of viral illness there is no impact or potential harm (similar to influenza) but the benefit is seen with the later hyperinflammatory phase. This trial was open-label, but mortality endpoint would tend to discount bias to a substantial degree. Women appeared to benefit less from dexamethasone than men.</p>
FLARE June 26	<p>Should we be using steroids in COVID-19? Yes. Recently released, preliminary, (not yet peer-reviewed) data from the RECOVERY trial demonstrate that dexamethasone has a mortality benefit in COVID-19 patients requiring oxygen or mechanical ventilation and should likely be used.</p> <p>Prior studies on steroids in ARDS suggested heterogeneous effects, with benefit for some subgroups and harm for others. In particular, observational data on influenza suggests increased mortality with steroid use in viral pneumonia and ARDSnet RCT data suggests harm in patients greater than 13 days from ARDS onset.</p> <p>Observational data is subject to potential confounding by indication. RCT data from RECOVERY should allay some concerns about harm from low dose steroid use in COVID-19.</p> <p>Although significant questions remain in regards to longer-term follow-up, use of concurrent medications in the control arm, and further identification of potential effect modifiers, clinicians should strongly consider the use of dexamethasone in their COVID-19 patients with an oxygen requirement or hypoxemic respiratory failure.</p>
CEBM June 26	<p>Shang et al published the views of Chinese experts who had treated COVID-19 in Wuhan. They stated that “systemic corticosteroids should probably not be used for the treatment of COVID-19. For critically ill patients with ARDS at an early stage, corticosteroids should probably be prudently used at a low or moderate dose over the short course if there are no contraindications (Grade 2–, weak recommendation).”</p> <p>There was weak supporting evidence from non-randomized trials. A cohort study of 201 patients from Wuhan showed that in the 84 patients who developed ARDS (42%), “treatment with methylprednisolone decreased the risk of death (HR, 0.38; 95% CI, 0.20–0.72).” A retrospective assessment of 46 severely ill Chinese patients showed that COVID-19 resolved more rapidly in the 26 patients given low-dose methylprednisolone. A US retrospective examination of data from patients treated with methylprednisolone and historical controls suggested that active treatment halved mortality. A similar French study, with propensity score matching, gave similar results.</p> <p>We now have preliminary results from the dexamethasone arm of the UK RECOVERY Trial. The NHS Central Alerting System posted a letter from the UK’s four Chief Medical Officers and the Director of NHS England, providing scanty details. (†)</p> <p>The data were then published in the RECOVERY investigators’ preprint posted on medRxiv, typically marked “not certified by peer review”, on 22 June 2020. The primary endpoint was 28-day mortality. The analysis showed that</p>

Reviewer	Findings
	<p>dexamethasone reduced mortality significantly, both overall and in those receiving oxygen treatment only or invasive ventilation. However, the relative risk of dying at 28 days was non-significantly increased in those with mild disease who did not require oxygen: relative risk 1.22 (95% CI 0.93–1.61), and there was a significant trend in relative risk reduction across the three categories of severity: $\chi^2=11.49$; $P<0.001$. This implies that dexamethasone treatment is life-saving in patients with COVID-19 severe enough to need oxygen therapy, with or without ventilatory support, but may be harmful in patients with mild disease.</p> <p>The UK's Chief Medical Officers also wrote, "Normally we would advise waiting for the full paper before changing practice, to ensure final analysis and peer review do not lead to different conclusions. However, given this clear mortality advantage, with good significance [sic], and with a well known medicine which is safe [sic] under these circumstances we consider it is reasonable for practice to change in advance of the final paper."</p> <p>However, apart from the concern about the outcome in those who did not receive oxygen, other questions remain, such as the effects of co-medications (e.g. NSAIDs) in the different groups.</p>
<p>SIDP June 24</p>	<p>The role of corticosteroids in COVID-19 is controversial.</p> <p>Low dose dexamethasone was found in one RCT to significantly reduce mortality in COVID-19 patients requiring respiratory support</p> <p>No evidence of benefit and concern of potential harm in patients not requiring respiratory support</p> <p>Multiple RCTs are ongoing</p>

†—details of the design and results of the RECOVERY trial omitted

Medical center guidance on corticosteroids

Hospital	Recommendation
<p>Penn Medicine July 24 [see note]</p>	<p>For patients on mechanical ventilation, dexamethasone is strongly recommended.</p> <p>For critically ill patients, dexamethasone is strongly recommended in patients with compelling indications including patients with refractory septic shock and obstructive lung disease and in patients who require high-flow nasal oxygen or non-invasive ventilation.</p> <p>For hospitalized patients with moderate- to severe illness requiring supplemental oxygen, consider dexamethasone if the potential benefits are deemed to outweigh risks, factoring in comorbidities, risk of progression, and clinical trajectory as well as data suggesting potential trend toward harm in patients not on supplemental oxygen. Of note, patients with duration of symptoms ≤ 7 days have no demonstrated benefit from dexamethasone.</p> <p>For patients who do not require supplemental oxygen, we strongly recommend against using dexamethasone, but corticosteroids should not be withheld from these patients if there is a separate indication such as obstructive lung disease or refractory shock.</p> <p>Dexamethasone should not be continued after discharge unless there is another compelling reason to do so.</p> <p><i>CEP NOTE: There are two guidance documents based on the same evidence analysis (link 1, link 2).</i></p>
<p>Yale July 24</p>	<p>For hospitalized patients requiring oxygen supplementation, give dexamethasone 6 mg PO for 7 days or until discharge if discharged before 7 days. Also give remdesivir for 5 days. Corticosteroids may be helpful in attenuating cytokine release in patients with severe disease.</p>
<p>Brigham July 19</p>	<p>We recommend strong consideration of low-dose systemic steroids for COVID+ patients who are critically ill or require supplemental oxygen. This is based on emerging but as yet not peer-reviewed evidence of a mortality benefit in a subset of hospitalized patients with COVID-19, suggesting that the benefits of systemic corticosteroids are likely to outweigh the risks at this dose.</p> <p>Dosing regimens to consider include:</p> <ul style="list-style-type: none"> Dexamethasone 6mg IV or PO daily x 10 days Hydrocortisone 50mg IV Q8h x 10 days Methylprednisolone 15mg IV BID x 10 days Prednisone 40mg PO daily x 10 days <p>If also treating shock, we recommend hydrocortisone 50mg IV Q6h until improvement in shock followed by consideration of steroid dosing as above to complete 10 days of total treatment. Indications for steroids in shock include: any shock in a patient with chronic steroid use >10mg prednisone daily, or multipressor (>2 pressor) shock without history of chronic steroid use.</p>

Hospital	Recommendation
Mass General July 1	<p>Dexamethasone is recommended for hospitalized patients with severe COVID-19 (requiring supplementary oxygen). Systemic steroids should be avoided for patients with mild or moderate disease (no oxygen support) unless there is another indication.</p> <p>No data are available for the combination of dexamethasone and remdesivir at this time.</p> <p>Dexamethasone is a moderate CYP3A4 inducer; review of potential drug-drug interactions is recommended before initiation. Coadministration with remdesivir is allowable.</p> <p>Dexamethasone has fetal effects; please refer to pregnancy section for specific guidance.</p> <p>Contraindications to dexamethasone use include previous hypersensitivity and uncontrolled fungal infection.</p> <p>Close monitoring for hyperglycemia is recommended, particularly in a person with diabetes mellitus.</p>
UCSF July 1	<p>Recommendations about steroids are forthcoming. In the meantime, steroids can be considered on a case by case basis.</p>
Ontario June 29	<p><u>Critically ill patients</u>: Dexamethasone 6 mg po/iv daily for 10 days (or until discharge if sooner) is recommended.</p> <p><u>Moderately ill patients</u>: Dexamethasone 6 mg po/iv daily for 10 days (or until discharge if sooner) is recommended.</p> <p><u>Mildly ill patients</u>: Dexamethasone is not recommended.</p> <p>Other corticosteroids should not be offered to patients with COVID-19 outside of approved clinical trials unless there are other indications for corticosteroid use.</p>

CEP note: there is also a protocol distributed by the Eastern Virginia Medical School Medical Group, but reviewers from Penn Medicine and CEP staff consider much of it to be unsupported by the evidence.

Guidance sources

- ASHP—American Society of Health System Pharmacists
- ATS—American Thoracic Society
- Australia— National COVID-19 Clinical Evidence Taskforce (27 member organizations)
- Canada—Canadian Ministry of Health
- CCCS—Canadian Critical Care Society
- DoD—Defense Health Agency, US Department of Defense.
- EEF—Evidence Ecosystem Foundation
- IDSA—Infectious Disease Society of America
- NIH—National Institutes of Health COVID-19 Treatment Guidelines Panel
- NICE—National Institute for Health and Care Excellence (UK National Health Service)
- Ontario—Sinai Health System/University Health Network Antimicrobial Stewardship Program
- WHO—World Health Organization

Update history (key additions and changes only)

- July 27: Many guidelines have been updated in response to preliminary reports from the RECOVERY trial.
 - New systematic review from VA-ESP. Evidence reviews not specific to COVID-19 removed.
 - Substantial changes in conclusions favor use of corticosteroids in patients requiring oxygen.
- June 8: Initial report.

About this report

A Rapid Guidance Summary is a focused synopsis of recommendations from selected guideline issuers and health care systems, intended to provide guidance to Penn Medicine providers and administrators during times when latest guidance is urgently needed. It is not based on a complete systematic review of the evidence. Please see the CEP web site (<http://www.ups.upenn.edu/cep>) for further details on the methods for developing these reports.

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