COVID-19: Corticosteroids For Hospitalized Patients

A Rapid Guidance Summary from the

Penn Medicine Center for Evidence-based Practice

Last updated June 8, 2020. All links rechecked June 8 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 and treatment of patients who are pregnant is outside the scope of this report.*

Summary of Major Recommendations

- Guidelines recommend against routine use of corticosteroids in patients with COVID-19 disease.
- Guidelines weakly recommend using corticosteroids in patients with acute respiratory distress syndrome (ARDS) from severe COVID-19 disease.
- There is little direct evidence on the safety and effectiveness of corticosteroids in patients with COVID-19 disease. The most recent review concluded that corticosteroids reduce mortality in patients with COVID-19 related ARDS and increase mortality in patients without ARDS, but the strength of the evidence was very low.
- Some but not all health systems are recommending corticosteroids to COVID-19 patients with ARDS.

Public Health Agency and Professional Society Guidelines on Corticosteroids

Source	Recommendations
Australia June 3	Avoid corticosteroids in people with suspected or confirmed COVID-19 unless there is an evidence-based indication for them (e.g. severe acute exacerbation of COPD or asthma). (based on expert opinion) CEP NOTE: this guidance is for patients with moderate to severe disease; guidance for patients with severe to critical disease do not include recommendations for or against corticosteroids.
WHO May 27	We recommend against the routine use of systemic corticosteroids for treatment of viral pneumonia.
CCCS May 19	In patients with severe COVID-19 and ARDS we suggest using corticosteroids (Weak recommendation). In patients with severe COVID-19 who do not have ARDS we suggest NOT using corticosteroids (Weak recommendation).
DoD May 14	There is a strong consideration to avoid routine steroids based on early data out of China as well as other studies related to Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) which have shown that steroids delay viral clearance. However, new consensus guidelines recommend considering methylprednisolone for intubated COVID-19 patients with ARDS.

NIH May 12	<u>For critically ill patients with COVID-19:</u> The Panel recommends against the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without acute respiratory distress syndrome (ARDS) (strong recommendation based on expert opinion). For mechanically ventilated patients with ARDS, there is insufficient evidence to recommend for or against the use of systemic corticosteroids (optional recommendation based on RCT evidence). For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (i.e., shock reversal) over no corticosteroids (moderate recommendation based on non-randomized studies). <u>For hospitalized, non-critically ill patients with COVID-19:</u> The Panel recommends against the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized patients, unless they are in the intensive care unit (strong recommendation based on expert opinion). *CEP NOTE: additional guidance available for patients on corticosteroids for a chronic condition.*
NICE April 23	Do not routinely offer a corticosteroid unless the patient has other conditions for which these are indicated, such as asthma or COPD.
IDSA April 21	Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence) Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)
ATS April 3	For hospitalized patients with COVID19 who have evidence of pneumonia, we make no suggestion either for or against treatment with systemic corticosteroids. 15% of panel favored intervention, 18% made no suggestion, and 67% against intervention.
Canada April 2	Do not routinely give systemic corticosteroids for treatment of viral pneumonia outside of clinical trials.
Surviving Sepsis March 21	For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy (“shock- reversal”), over no corticosteroid therapy (weak recommendation, low-quality evidence). A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200mg per day administered either as an infusion or intermittent doses. In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we suggest against the routine use of systemic corticosteroids (weak recommendation, low-quality evidence). In mechanically ventilated adults with COVID-19 and ARDS, we suggest using systemic corticosteroids, over not using corticosteroids (weak recommendation, low-quality evidence). Remark: The majority of our panel support a weak recommendation (i.e., suggestion) to use steroids in the sickest patients with COVID-19 and ARDS. However, because of the very low-quality evidence, some experts on the panel preferred not to issue a recommendation until higher quality direct evidence is available.

Rapid Evidence Reviews on Corticosteroids

Reviewer	**Findings**
PennMedicine June 8	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. *CEP NOTE: the full review includes summaries of each of the individual studies plus additional information on the limitations of the available evidence.*

ASHP June 3 (general)	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. NIH, CDC, WHO, IDSA, and other experts have issued guidelines for the use of corticosteroids in patients with COVID19 based on the currently available information. Recommendations are made according to the severity of illness, indications, and underlying medical conditions and should be considered on a case-by-case basis. General recommendations: WHO, CDC, NIH, and IDSA generally recommend against the routine use of corticosteroids for the treatment of COVID-19 unless indicated for another reason (e.g., asthma or COPD exacerbation, refractory septic shock). Non-critical patients: Corticosteroids generally should not be used in the treatment of early or mild disease since the drugs can inhibit immune response, reduce pathogen clearance, and increase viral shedding. NIH recommends against the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized patients unless they are in the intensive care unit. Critically ill patients: The Surviving Sepsis Campaign recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS). However, these experts generally support a weak recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS. NIH also recommends against the routine use of systemic corticosteroids for the treatment of mechanically ventilated COVID-19 patients without ARDS. However, the NIH panel states that there is insufficient evidence for or against the use of systemic corticosteroids in mechanically ventilated patients with COVID-19 and ARDS. IDSA suggests against using corticosteroids in hospitalized patients with COVID -19 pneumonia; however, in those with ARDS due to COVID- 19, systemic corticosteroids may be used in the context of a clinical trial. *CEP NOTE: Please see full ASHP evidence table for additional recommendations for patients in cytokine storm, patients in septic shock, and patients receiving corticosteroid therapy for chronic conditions.*
BMJ Best Practice June 3	Surviving Sepsis Campaign guidelines suggest that adults with ARDS who are receiving mechanical ventilation and adults with refractory shock should receive corticosteroids, although this recommendation is based on weak evidence. US National Institutes of Health guidelines say that there is insufficient evidence to recommend for or against the use of systemic corticosteroids in mechanically ventilated patients with ARDS. Other guidelines do not routinely recommend systemic corticosteroids for the treatment of COVID-19 unless they are indicated for another reason (e.g., exacerbation of asthma or chronic obstructive pulmonary disease, septic shock, ARDS) and then only after a risk/benefit analysis, or used in the context of a clinical trial. A meta-analysis of over 5000 patients found that corticosteroid treatment in patients with COVID-19 was associated with longer hospital stays and a higher rate of mortality.
Hopkins June 1	A study from a multi-hospital health system in Michigan compared outcomes in patients who were admitted for COVID-19 treatment before or after the adoption of a protocol for early corticosteroid treatment. Before the protocol was implemented, 56.8% of 81 patients received corticosteroids; after, 68.2% of 132 patients received steroids. Of those, 12.4% received steroids within the first 48 hours of hospitalization before the protocol was adopted; after, 41.7% received them within the first 48 hours. The primary composite outcome of death, respiratory failure requiring mechanical ventilation, or escalation to ICU care within 14 days of hospitalization occurred among 54.3% in the pre-protocol period and 34.9% after the early steroid protocol was adopted. The before-after study design implemented during a rapidly evolving epidemic limits the value of these findings. There were differences in the patient populations during the 2 periods; for example, 18.5% of patients in the pre- protocol group had chronic obstructive pulmonary disease compared to 9.1% in the post-protocol group. In addition, clinicians became more experienced, which can lead to changes in practice, and testing became more efficient, which allowed for more rapid diagnosis of COVID-19 and may have led to earlier hospital admission.
WHO May 27	A systematic review and meta-analysis of the impact of corticosteroid therapy on outcomes of persons with SARS- CoV-2, SARS-CoV and MERS-CoV revealed corticosteroids did not significantly reduce the risk of death, did not reduce hospitalization duration, ICU admission rate and/or use of mechanical ventilation, and had several adverse effects. A systematic review of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes and delayed viral clearance). A systematic review of observational studies in influenza found a higher risk of mortality and secondary infections with corticosteroids; the evidence was judged as very low to low quality owing to confounding by indication. A subsequent study that addressed this limitation by adjusting for time-varying confounders found no effect on mortality. Finally, a study of patients receiving corticosteroids for MERS used a similar statistical approach and found no effect of corticosteroids on mortality but delayed LRT clearance of MERS-CoV. Given the lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason. Other reasons may include exacerbation of asthma or chronic obstructive pulmonary disease (COPD), septic shock or ARDS, and risk/benefit analysis needs to be conducted for individual patients.
ASHP May 21	Evidence on methylprednisolone Findings from observational studies suggest that for patients with COVID-19 pneumonia who progress to ARDS, methylprednisolone treatment may be beneficial. However, results should be interpreted with caution because of potential bias (drug used in sickest patients) and small sample size. Confirmation from randomized controlled studies is needed.

Published systematic reviews on corticosteroids

Reviewer	Findings
Reviews specific to COVID-19 patients	
EEF May 3	For patients with COVID-19 disease and ARDS, corticosteroids reduce mortality from 618 per 1,000 to 326 per 1,000 (summary hazard ratio 0.41, 95% CI 0.20-0.83, 1 study, 84 patients). Evidence grade very low due to high imprecision. For patients with COVID-19 disease and no ARDS, corticosteroids increase mortality from 104 per 1,000 to 223 326 per 1,000 (summary hazard ratio 2.30, 95% CI 1.00-5.29, 2 studies, 331 patients). Evidence grade very low due to high imprecision. *CEP NOTE: Please see linked document for living evidence review including results for other outcomes that were based on indirect evidence.*
Veronese April 24	The literature to date does not fully support the routine use of corticosteroids in COVID-19, but some findings suggest that methylprednisolone could lower mortality rate in more severe forms of the condition. 4 studies met inclusion criteria. Studies too heterogeneous for quantitative data synthesis. *CEP NOTE: all cited studies involved COVID-19 patients.*
Reviews combining studies of COVID-19 patients and studies of patients with other viral respiratory diseases	
Yi May 1	Corticosteroids may reduce mortality for patients with COVID-19 and ARDS. For patients with severe COVID-19 but without ARDS, evidence regarding benefit is inconsistent and of very low quality. CEP NOTE: this is the published version of the “living evidence review” referenced above
Li April 22	Corticosteroid use in subjects with SARS-CoV-2, SARS-CoV, and MERS-CoV infections delayed virus clearing and did not convincingly improve survival, reduce hospitalization duration or ICU admission rate and/or use of mechanical ventilation. There were several adverse effects. Because of a preponderance of observational studies in the dataset and selection and publication biases our conclusions, especially regarding SARS- CoV-2, need confirmation in a randomized clinical trial. In the interim we suggest caution using corticosteroids in persons with COVID-19.
Yang March 31	Corticosteroid treatment was associated with higher risk of mortality. Summary risk ratio 2.36, 95% CI 1.31-4.28, I2 = 29%, 2 studies (0 randomized), 179 patients. *CEP NOTE: Results of this analysis are cofounded by pooling of critical care and non-critical care patients, and by differences in patient characteristics that could have affected the decision to use corticosteroids.*

Hospital Guidance on Corticosteroids

Hospital	Recommendation
Penn Medicine June 8	For critically ill and intubated patients, corticosteroids are recommended in patients with compelling indications including patients with refractory septic shock and obstructive lung disease. Corticosteroids can be considered in patients with ARDS when potential benefits outweigh risks and after discussion with infectious diseases and pulmonary [specialists].
Brigham June 5	At this time, we do not recommend steroids for COVID-19 except as part of a clinical trial or if treating another indication such as asthma or COPD exacerbation.
Michigan June 3	Limited evidence supporting routine use of corticosteroids: Prior studies assessing outcomes in patients receiving systemic corticosteroids for infections due to closely related viruses (SARS-CoV and MERS-CoV) found a lack of effectiveness and possible harm. However, early published and unpublished observations from China suggest that corticosteroids may reduce mortality in COVID-19 infected patients with ARDS and evidence of progression. If steroids are contemplated, it is recommended to use moderate doses of methylprednisolone (1-2 mg/kg) for 3-5 days.
Yale May 27	For patients with severe disease and worsening ARDS after 48 hours, consider methylprednisolone 40 mg q8h for 72 hours. Reassess for extended course or taper (up to 5-7 days total). Corticosteroids may be helpful in attenuating cytokine release in patients with severe disease.
Washington May 20	Routine use of steroids is not recommended at this time. Use of steroids in patients with severe disease (requiring oxygen support or mechanical ventilation) could be considered as part of the supportive care regimen for patients with ARDS on a case-by-case basis.

Kentucky May 16	Limited data is available regarding the utility of steroids in the treatment of COVID-19. Methylprednisolone can be considered in patients requiring 4L or more of O2/min or with escalating oxygen requirements from baseline at a dose of 0.5-1 mg/kg/day in 2 divided doses for 3 days (up to 7 in ICU patients) based on data from trial highlighted below. Benefit seen with early administration (48 hours from admission). Consider a maximum of 80mg IV q12h for obese patients. Study looking at early short course corticosteroids in hospitalized patients with COVID-19 was published (see Hopkins evidence review above for description of this study)
Mt. Sinai May 4	Not recommended at this time.

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)

Surviving Sepsis Campaign– joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine

WHO–World Health Organization

Update history (key additions and changes only)

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.uphs.upenn.edu/cep) for further details on the methods for developing these reports.

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