Corticosteroids

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Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen, presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. In contrast, in hospitalized patients with COVID-19 who do not require supplemental oxygen, the use of systemic corticosteroids has not shown any benefits and may cause harm. The COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations for the use of corticosteroids in hospitalized patients with COVID-19 are based on results from these clinical trials (see Tables 4a and 4b for more information). There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19.

Recommendations

For Nonhospitalized Adults With COVID-19

- See Therapeutic Management of Nonhospitalized Adults With COVID-19 for the Panel’s recommendations on the use of dexamethasone or other systemic corticosteroids in certain nonhospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19 in these patients.
- Patients with COVID-19 who are receiving dexamethasone or another corticosteroid for an underlying condition should continue this therapy as directed by their health care provider (AIH).

For Hospitalized Adults With COVID-19

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel’s recommendations on the use of dexamethasone or other systemic corticosteroids in certain hospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19 in these patients.

Systemic Corticosteroids in Patients With COVID-19

Nonhospitalized Adults

There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19. Therefore, the safety and efficacy of using systemic corticosteroids in this population have not been established. Generally, the use of systemic corticosteroids is associated with adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting. For more information, see General Management of Nonhospitalized Patients With Acute COVID-19.

Hospitalized Adults

The RECOVERY trial was a multicenter, open-label trial in the United Kingdom that randomly assigned 6,425 hospitalized patients to receive up to 10 days of dexamethasone 6 mg once daily plus standard care or standard care alone. Mortality at 28 days was lower among the patients who received
Dexamethasone than among those who received standard care alone. This benefit of dexamethasone was observed in patients who were mechanically ventilated or who required supplemental oxygen at enrollment; in contrast, no benefit was seen in patients who did not require supplemental oxygen at enrollment.

The CoDEX trial was a multicenter, open-label trial in Brazil that evaluated dexamethasone in patients who were mechanically ventilated due to acute respiratory distress syndrome (ARDS) induced by COVID-19. Although the trial was terminated early, the study results support the RECOVERY trial finding that systemic corticosteroids are beneficial in hospitalized patients with COVID-19. The trial randomly assigned 299 patients to receive either standard care plus intravenous (IV) dexamethasone 20 mg once daily for 5 days and then dexamethasone 10 mg IV once daily for 5 days or standard care alone. The mean number of days alive and free from mechanical ventilation over 28 days was greater in the dexamethasone arm than in the standard care alone arm. However, there were no differences between the arms in 28-day mortality, the mean number of intensive care unit-free days at 28 days, or the mean duration of mechanical ventilation at 28 days.

An observational study evaluated the use of corticosteroids in 15,404 hospitalized patients with positive SARS-CoV-2 polymerase chain reaction results or antigen test results from the Department of Veteran Affairs’ database. Corticosteroids were administered to 60% of the patients within 48 hours of admission, and 95% of the patients who received corticosteroids received dexamethasone. A total of 9,450 patients did not receive supplemental oxygen during the study. Of these patients, 3,514 (37%) received dexamethasone, administered for a median duration of 5 days (IQR 3–8 days). Using average treatment effect estimates, patients who received dexamethasone without supplemental oxygen had an increased risk of death within 90 days (HR 1.76; 95% CI, 1.47–2.12). Patients who received dexamethasone either without supplemental oxygen or with low-flow nasal cannula oxygen had a 60% higher risk of death. Although this study was observational, the investigators employed several statistical techniques to minimize potential bias, including propensity scoring and weighted analyses. Additionally, several subgroup and sensitivity analyses in this study confirmed the overall results.

**Dose of Dexamethasone**

The COVID STEROID 2 trial is the largest study to date that has investigated the use of different doses of corticosteroids in people with COVID-19. This multicenter trial randomized hospitalized patients to receive up to 10 days of once-daily dexamethasone 6 mg (n = 485) or dexamethasone 12 mg (n = 497). The median number of days alive without life support at 28 days after randomization was 20.5 days in the dexamethasone 6 mg arm (IQR 4.0–28.0 days) and 22.0 days in the dexamethasone 12 mg arm (IQR 6.0–28.0 days), yielding an adjusted mean difference of 1.3 days (95% CI, 0–2.6; $P = 0.07$). No differences were found in 28- or 90-day mortality between the arms. Approximately 12% of the patients in each arm received either an interleukin-6 inhibitor or a kinase inhibitor during the study. While these conventional analyses did not reach statistical significance, a preplanned Bayesian analysis found a higher probability of benefit and a lower probability of harm for the 12-mg dose than for the 6-mg dose.

A smaller randomized controlled trial reported a shorter time to clinical improvement and a lower frequency of adverse events in patients with COVID-19 who received a lower dose of dexamethasone (8 mg IV once daily) compared to those who received higher doses (8 mg IV 2 or 3 times daily). A lower proportion of patients in the low-dose group died within 60 days compared to the intermediate- and high-dose groups (17% vs. 30% and 41%, respectively; $P = 0.06$). It is worth noting that this study included <200 participants.

A third small, open-label, randomized trial (with <100 participants) found no difference in the median number of ventilator-free days at 28 days after randomization between patients who received higher...
doses of dexamethasone (16 mg IV daily for 5 days, followed by 8 mg daily for 5 days) and those who received lower doses (6 mg IV daily for 10 days).\textsuperscript{9}

The mixed results from these studies have led the Panel to continue to recommend 6 mg once daily as the preferred dose for dexamethasone. However, the Panel notes that both the traditional and Bayesian analyses conducted during the COVID STEROID 2 trial suggest that the 12-mg dose might confer a benefit in patients who require high levels of respiratory support. As a result, some clinicians might choose to use the higher dose of dexamethasone in these patients. It should be noted that there are currently no data evaluating the safety and efficacy of using lower or higher doses of corticosteroids in combination with other immunomodulators to treat COVID-19.

\textit{Combination Immunomodulator Therapy}

Using systemic corticosteroids in combination with other agents, including tocilizumab (see \textit{Interleukin-6 Inhibitors})\textsuperscript{10,11} or baricitinib (see \textit{Kinase Inhibitors}),\textsuperscript{12} has been shown to have a clinical benefit in subsets of hospitalized patients with COVID-19, especially those with early critical illness and/or those with signs of systemic inflammation. For the Panel’s recommendations on when to use dexamethasone with another immunomodulator, see \textit{Therapeutic Management of Hospitalized Adults With COVID-19}.

Please see Tables \textit{4a} and \textit{4b} for data from clinical trials that have evaluated the use of corticosteroids in patients with COVID-19.

\textit{Systemic Corticosteroids Other Than Dexamethasone}

Systemic corticosteroids other than dexamethasone, including hydrocortisone\textsuperscript{13,14} and methylprednisolone,\textsuperscript{15,16} have been studied for the treatment of COVID-19 in several randomized trials. Some of these trials were stopped early due to under-enrollment following the release of the RECOVERY trial results. Consequently, the sample size of many these trials was insufficient to assess efficacy (i.e., there were too few events to definitively confirm or exclude an effect, although many point estimates suggested a beneficial effect). Therefore, the evidence supporting the use of hydrocortisone or methylprednisolone for the treatment of COVID-19 is not as strong as the evidence supporting the use of dexamethasone. Based on the available evidence, the Panel has concluded the following:

- If dexamethasone is not available, alternative glucocorticoids (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (orally or IV)\textsuperscript{17} are:
  - Prednisone 40 mg
  - Methylprednisolone 32 mg
  - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
  - \textit{Long-acting corticosteroid}: Dexamethasone; half-life 36 to 72 hours, administer once daily.
  - \textit{Intermediate-acting corticosteroids}: Prednisone and methylprednisolone; half-life 12 to 36 hours, administer once daily or in 2 divided doses daily.
  - \textit{Short-acting corticosteroid}: Hydrocortisone; half-life 8 to 12 hours, administer in 2 to 4 divided doses daily.
- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see \textit{Hemodynamics} for more information. Unlike other corticosteroids that have previously been
studied in patients with ARDS, dexamethasone lacks mineralocorticoid activity and thus its effects on sodium balance and fluid volume are minimal.\textsuperscript{18}

**Inhaled Corticosteroids in Patients With COVID-19**

Inhaled corticosteroids have been identified as potential COVID-19 therapeutic agents because of their targeted anti-inflammatory effects on the lungs. In addition, certain inhaled corticosteroids have been shown to impair viral replication of SARS-CoV-2\textsuperscript{19} and downregulate the expression of the receptors used for cell entry.\textsuperscript{20,21} Two open-label randomized controlled trials and 2 double-blind, placebo-controlled trials provide additional insights regarding the role of inhaled corticosteroids in outpatients with COVID-19, as described below and in Table 4b.

**Recommendation**

- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19.

**Rationale**

Inhaled budesonide was studied in 2 open-label randomized controlled trials in outpatients with mild symptoms of COVID-19.\textsuperscript{22,23} The small STOIC trial suggested that initiating inhaled budesonide in adult outpatients with mild COVID-19 may reduce the need for urgent care or emergency department assessment or hospitalization.\textsuperscript{22} PRINCIPLE, a larger, open-label trial in nonhospitalized patients with COVID-19 who were at high risk of disease progression, found that using inhaled budesonide did not affect the rate of hospitalization or death but did reduce the time to self-reported recovery.\textsuperscript{23} The findings from these trials should be interpreted with caution given the open-label design of the studies and other limitations.

Inhaled ciclesonide was studied in 2 double-blind, randomized, placebo-controlled trials in outpatients with mild COVID-19. The primary endpoint in 1 study was time to alleviation of COVID-19-related symptoms. In this study, the use of inhaled ciclesonide did not reduce the time to self-reported recovery, but the therapy did reduce the number of subsequent COVID-related emergency department visits or hospitalizations. The robustness of this conclusion is uncertain given the small number of events, which is likely due to the relatively small number of participants with comorbidities.\textsuperscript{24} In the smaller CONTAIN study, the combined use of inhaled and intranasal ciclesonide did not improve the resolution of fever and/or respiratory symptoms by Day 7.\textsuperscript{25}

The studies described above that evaluated the use of inhaled corticosteroid therapy in outpatients with mild COVID-19 have identified inconsistent effects of this therapy on subsequent hospitalization, and similar placebo-controlled trials have not demonstrated that this therapy improves the time to symptom resolution. The placebo-controlled studies did not enroll enough patients who were at high risk of disease progression; therefore, further studies in this population are needed. For additional information on these trials, see Table 4b.

**Monitoring, Adverse Effects, and Drug-Drug Interactions**

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for certain adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Patients who are receiving inhaled corticosteroids may develop oral candidiasis.
- The use of systemic corticosteroids may increase the risk of opportunistic fungal infections (e.g., mucormycosis, aspergillosis) and reactivation of latent infections (e.g., hepatitis B virus infection, herpesvirus infections, strongyloidiasis, tuberculosis).\textsuperscript{26-30}
• Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.\textsuperscript{31,32} Many clinicians would initiate empiric antiparasitic treatment (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients who currently reside or who have previously resided in areas where \textit{Strongyloides} is endemic (i.e., tropical, subtropical, or warm temperate areas).\textsuperscript{33}

• Using systemic corticosteroids with other immunosuppressants, such as tocilizumab or baricitinib, could theoretically increase the risk of secondary infections. However, clinical trials have reported no difference in the rates of secondary infections between patients who received corticosteroids in combination with another immunomodulatory agent and those who received corticosteroids alone.

• Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. Therefore, it could reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should carefully review a patient’s concomitant medications to assess the potential for drug-drug interactions.

• Using a CYP3A4 inhibitor with inhaled budesonide may lead to increased systemic absorption of budesonide, which may result in systemic adverse effects from the corticosteroid.

\textbf{Considerations in Pregnancy}

A short course of betamethasone or dexamethasone, which are both known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.\textsuperscript{34,35}

A short course of dexamethasone for the treatment of COVID-19 during pregnancy offers the potential benefit of decreased maternal mortality and a low risk of fetal adverse effects. Therefore, the Panel recommends using \textbf{dexamethasone} in hospitalized pregnant patients with COVID-19 who are mechanically ventilated (AIII) or who require supplemental oxygen but are not mechanically ventilated (BIII).

\textbf{Considerations in Children}

The safety and effectiveness of using dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Caution is warranted when using data from clinical trials that enrolled adults to inform treatment recommendations for children, particularly younger children and those who are less severely ill. The Panel recommends using \textbf{dexamethasone} for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (BIII). Corticosteroids are not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., administered via a nasal cannula only) but could be considered on a case-by-case basis. The use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated and may be harmful; therefore, such use should be considered only if the benefit is expected to outweigh the risks. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg per dose (with a maximum dose of 6 mg) once daily for up to 10 days. There is insufficient evidence to recommend either for or against the use of inhaled corticosteroids in pediatric patients with COVID-19.

\textbf{Methylprednisolone} or another corticosteroid should be used in combination with IV immunoglobulin for the initial treatment of multisystem inflammatory syndrome in children (MIS-C) (AIIb). The dosing regimen for initial therapy is methylprednisolone 1 to 2 mg/kg IV once daily or another glucocorticoid at an equivalent dose. See \textit{Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Children (MIS-C))}.
Syndrome in Adults [MIS-A]) for more information on the management of MIS-C.

Clinical Trials

Several clinical trials that are evaluating the use of corticosteroids for the treatment of COVID-19 are underway or in development. Please see ClinicalTrials.gov for the latest information.

References


