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,1 presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. There is no observed benefit of systemic corticosteroids in hospitalized patients with COVID-19 who do not require supplemental oxygen.2 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 Patients 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.

For Hospitalized Patients 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.

Systemic Corticosteroids in Patients With COVID-19

Nonhospitalized Patients

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

Hospitalized Patients

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 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.2 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. For additional information on the RECOVERY trial, see Table 4a.

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 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, ICU-free days over 28 days, or duration of mechanical ventilation at 28 days. See Table 4a for additional information.

Systemic corticosteroids used in combination with other agents, including other immunomodulators such as tocilizumab (see Interleukin-6 Inhibitors) or baricitinib (see Kinase Inhibitors), have demonstrated clinical benefit in subsets of hospitalized patients with COVID-19, especially those with early critical illness and/or with signs of systemic inflammation. For the Panel’s recommendations on when to use dexamethasone with another immunomodulator, see Therapeutic Management of Hospitalized Adults With COVID-19.

Please see Tables 4a and 4b for data from clinical trials evaluating corticosteroid use for COVID-19.

**Systemic Corticosteroids Other Than Dexamethasone**

Systemic corticosteroids other than dexamethasone, including hydrocortisone and methylprednisolone, 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 of 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, if true, suggested a beneficial effect). Therefore, evidence to support the use of hydrocortisone or methylprednisolone for the treatment of COVID-19 is not as strong as 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 (oral or IV) are:
  - Prednisone 40 mg
  - Methylprednisolone 32 mg
  - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
  - **Long-acting corticosteroid:** Dexamethasone; half-life 36 to 72 hours, administer once daily.
  - **Intermediate-acting corticosteroids:** Prednisone and methylprednisolone; half-life 12 to 36 hours, administer once daily or in 2 divided doses daily.
  - **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 Hemodynamics for more information. Unlike other corticosteroids previously studied in patients
with ARDS, dexamethasone lacks mineralocorticoid activity and thus has minimal effect on sodium balance and fluid volume.\textsuperscript{12}

**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{13} and downregulate expression of the receptors used for cell entry.\textsuperscript{14,15} 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{16,17} The small STOIC trial suggested that initiation of inhaled budesonide in adult outpatients with mild COVID-19 may reduce the need for urgent care or emergency department assessment or hospitalization.\textsuperscript{16} PRINCIPLE, a larger, open-label trial in nonhospitalized patients with COVID-19 at high risk of disease progression, found that use of inhaled budesonide did not affect the rate of hospitalization or death but did reduce the time to self-reported recovery.\textsuperscript{18} 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{19} 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{20}

The above-described studies of inhaled corticosteroid therapy for outpatients with mild COVID-19 have identified inconsistent effects of the therapy on subsequent hospitalization, and similar placebo-controlled trials have not demonstrated that this therapy results in improvements in symptom resolution. The placebo-controlled studies did not enroll enough patients at high risk of disease progression, and 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{21-25}
• Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.26,27 Many clinicians would initiate empiric antiparasitic treatment (e.g., with ivermectin) with or without serologic testing in patients from areas where *Stronglyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).28

• Using systemic corticosteroids with other immunosuppressants, such as tocilizumab or baricitinib, could theoretically increase the risk of secondary infections. However, this adverse effect has not been reported in clinical trials to date.

• 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 review a patient’s medication regimen 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 of the corticosteroid.

**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.29,30

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 dexamethasone in hospitalized pregnant patients with COVID-19 who are mechanically ventilated (AIII) or who require supplemental oxygen but are not mechanically ventilated (BIII).

**Considerations in Children**

The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients and caution is warranted when extrapolating recommendations for adults to patients aged <18 years. The Panel recommends using 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 perceived to outweigh the risks. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days. There is insufficient evidence to recommend for or against the use of inhaled corticosteroids for pediatric patients with COVID-19. Corticosteroids are second to IV immunoglobulin as the most used therapy for the treatment of multisystem inflammatory syndrome in children (MIS-C).31,32 See Special Considerations in Children for more information on the management of MIS-C.

**Clinical Trials**

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


31. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA*. (Note: The last sentence is incomplete and may require further clarification.)