

# Systemic Corticosteroids

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The results of several randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen,<sup>1,2</sup> 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 provided no benefit and increased mortality.<sup>3,4</sup> The COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations for the use of systemic corticosteroids in hospitalized patients with COVID-19 are based on results from these clinical trials (see [Table 5a](#)). There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19.

## Recommendations

- The Panel **recommends against** the use of **dexamethasone** or other systemic corticosteroids to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen (**AIIb**).
- 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 with COVID-19.
- 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**).

## Rationale

### *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 [Therapeutic Management of Nonhospitalized Adults With 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.<sup>3</sup> 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.

Several clinical trials have evaluated the use of systemic corticosteroids in critically ill patients with COVID-19 who were on supplemental oxygen with or without mechanical ventilation. These trials reported that all-cause mortality at 28 days was lower in those who received systemic corticosteroids

than in those who received standard of care or placebo; however, some of these trials were terminated early.<sup>1</sup>

In addition to the randomized controlled trials, a large observational study evaluated the use of systemic corticosteroids in 15,404 hospitalized patients with positive SARS-CoV-2 polymerase chain reaction or antigen test results from a Department of Veterans Affairs database.<sup>4</sup> 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 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.

## Dexamethasone Dose

The RECOVERY platform trial studied the use of dexamethasone 6 mg once daily for up to 10 days,<sup>3</sup> which is currently the recommended dose for hospitalized adults with COVID-19 who require supplemental oxygen. Several other randomized controlled trials evaluated the role of higher doses of dexamethasone or other corticosteroids in hospitalized patients with different levels of respiratory support. The results of some key studies are summarized below.

### ***Patients Who Received Conventional Oxygen or No Supplemental Oxygen***

The RECOVERY platform trial included an additional study in which patients with COVID-19 and evidence of hypoxemia (i.e., they were receiving conventional supplemental oxygen or had an oxygen saturation <92% on room air) were randomized to receive usual care plus high-dose dexamethasone (20 mg once daily for 5 days, then 10 mg once daily for 5 days or until hospital discharge, whichever came first) or usual care alone, which included low-dose dexamethasone (usually 6 mg once daily for 10 days).<sup>5</sup> On May 11, 2022, the trial's independent data monitoring committee stopped enrolling patients receiving conventional oxygen therapy and those not receiving any supplemental oxygen. Among the 1,272 patients enrolled, 28-day mortality was higher in the high-dose dexamethasone arm than in the usual care arm (19% vs. 12%; rate ratio 1.59; 95% CI, 1.20–2.10;  $P = 0.0012$ ).

### ***Patients Who Received Noninvasive or Mechanical Ventilation***

The COVID STEROID 2 trial investigated the use of different doses of corticosteroids in patients with COVID-19 and severe hypoxemia.<sup>6</sup> In this multicenter trial, hospitalized patients who required at least 10 L/min of oxygen or mechanical ventilation were randomized to receive up to 10 days of dexamethasone 6 mg once daily ( $n = 485$ ) or dexamethasone 12 mg once daily ( $n = 497$ ). The median number of days alive without life support at 28 days after randomization was 20.5 days in the dexamethasone 6 mg arm and 22.0 days in the dexamethasone 12 mg arm, yielding an adjusted mean difference of 1.3 days (95% CI, 0–2.6;  $P = 0.07$ ). No differences between the arms were found for 28- or 90-day mortality. Although these conventional analyses did not quite reach statistical significance, a preplanned Bayesian analysis found that dexamethasone 12 mg had a higher probability of benefit and a lower probability of harm than dexamethasone 6 mg.<sup>7</sup>

In the COVIDICUS trial, patients with COVID-19 and acute hypoxemic respiratory failure were randomized to receive dexamethasone 6 mg once daily for 10 days ( $n = 276$ , of which 37 received

placebo prior to release of results from the RECOVERY trial)<sup>3</sup> or high-dose dexamethasone (i.e., 20 mg once daily for 5 days, then 10 mg once daily for 5 days; n = 270).<sup>8</sup> At baseline, 98 patients were receiving mechanical ventilation, 114 were receiving continuous positive airway pressure, 10 were receiving noninvasive ventilation (NIV), 199 were receiving high-flow nasal cannula oxygen, and 125 were receiving standard oxygen therapy through a nonrebreather mask. There was no difference in 60-day mortality between the arms (HR 0.96; 95% CI, 0.69–1.33; *P* = 0.79).

The mixed results from these studies have led the Panel to continue to recommend 6 mg once daily as the preferred dose of dexamethasone in hospitalized patients with COVID-19 who require supplemental oxygen, including patients receiving NIV or mechanical ventilation. However, the Panel notes that both the conventional and Bayesian analyses conducted during the COVID STEROID 2 trial suggest that a dose of 12 mg might confer a benefit in patients who require NIV or mechanical ventilation.<sup>6,7</sup> Most patients in the COVID STEROID 2 trial did not receive additional immunomodulators beyond corticosteroids.<sup>6</sup> Currently, there are no data from clinical trials that evaluated the safety and efficacy of using doses of dexamethasone that were larger or smaller than 6 mg once daily in combination with other immunomodulators to treat hospitalized adults with COVID-19.

### ***Combination Immunomodulator Therapy***

Using systemic corticosteroids in combination with other agents, including tocilizumab (see [Interleukin-6 Inhibitors](#)),<sup>9,10</sup> baricitinib (see [Janus Kinase Inhibitors](#)),<sup>11</sup> abatacept, or infliximab,<sup>12</sup> has been shown to have a clinical benefit in subsets of hospitalized patients with COVID-19, especially those who are in the early stages of critical illness and those 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](#).

See [Table 5a](#) for a summary of the data from clinical trials that have evaluated the use of systemic corticosteroids in patients with COVID-19.

### **Systemic Corticosteroids Other Than Dexamethasone**

Systemic corticosteroids other than dexamethasone, including hydrocortisone<sup>13,14</sup> and methylprednisolone,<sup>15,16</sup> have been studied for the treatment of COVID-19 in several randomized trials. Some of these trials were stopped early due to low enrollment following the release of the RECOVERY trial results. Consequently, the sample size 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 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 corticosteroids (e.g., **prednisone, methylprednisolone, hydrocortisone**) can be used (**BIII**).
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (orally or intravenously)<sup>17</sup> 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-lives 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 Adults](#) for more information. Unlike other corticosteroids that have previously been studied in patients with acute respiratory distress syndrome, dexamethasone lacks mineralocorticoid activity and, thus, its effects on sodium balance and fluid volume are minimal.<sup>18</sup>

## 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). The use of systemic corticosteroids may increase the risk of opportunistic fungal infections (e.g., aspergillosis, mucormycosis) and reactivation of latent infections (e.g., hepatitis B virus infection, herpes simplex virus and varicella zoster virus infections, strongyloidiasis, tuberculosis).<sup>19-26</sup> Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.<sup>24,27</sup> Many clinicians would initiate empiric treatment for strongyloidiasis (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 *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).<sup>28</sup>

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 3A4 inducer. Therefore, it could reduce the concentration and potential efficacy of concomitant medications that are cytochrome P450 3A4 substrates. Clinicians should carefully review a patient's concomitant medications to assess the potential for drug-drug interactions.

## Considerations in Pregnant and Lactating People

See [Pregnancy, Lactation, and COVID-19 Therapeutics](#) for the Panel's guidance regarding the use of dexamethasone during pregnancy and lactation.

## Considerations in Children

Dexamethasone is recommended for hospitalized children with COVID-19 who require supplemental oxygen. See [Therapeutic Management of Hospitalized Children With COVID-19](#) for the Panel's recommendations. Methylprednisolone or another corticosteroid is recommended for the treatment of multisystem inflammatory syndrome in children (MIS-C). See [Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A](#) for the Panel's recommendations.

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