# Therapeutic Management of Hospitalized Adults With COVID-19

**Table 2b. Therapeutic Management of Hospitalized Adults With COVID-19**

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Recommendations for Antiviral or Immunomodulator Therapy</th>
<th>Recommendations for Anticoagulant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalized for Reasons Other Than COVID-19</strong></td>
<td>Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19(^{a,b})</td>
<td>See <a href="https://www.covid19treatmentguidelines.nih.gov/">Therapeutic Management of Nonhospitalized Adults With COVID-19</a>.</td>
</tr>
<tr>
<td><strong>Hospitalized but Does Not Require Oxygen Supplementation</strong></td>
<td>All patients</td>
<td>For patients without an indication for therapeutic anticoagulation: * <strong>Prophylactic dose of heparin</strong>, unless contraindicated (AI); (BIII) for pregnant patients</td>
</tr>
<tr>
<td><strong>Hospitalized and Requires Conventional Oxygen</strong></td>
<td>Patients who require minimal conventional oxygen</td>
<td>Remdesivir(^d) (BII)</td>
</tr>
<tr>
<td></td>
<td>Most patients</td>
<td>Use <strong>dexamethasone plus remdesivir</strong> (BII). If remdesivir cannot be obtained, use <strong>dexamethasone</strong> (BII).</td>
</tr>
<tr>
<td></td>
<td>Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation</td>
<td>Add <strong>PO baricitinib</strong>(^e) (BII) or <strong>IV tocilizumab</strong>(^f) (BII) to 1 of the options above.</td>
</tr>
<tr>
<td><strong>Hospitalized and Requires HFNC Oxygen or NIV</strong></td>
<td>All patients</td>
<td>Dexamethasone should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in order of preference): * <strong>PO baricitinib</strong>(^i) (AI) * <strong>IV tocilizumab</strong>(^i) (BII) Add remdesivir to 1 of the options above in certain patients (for examples, see footnote).(^j)</td>
</tr>
<tr>
<td><strong>Hospitalized and Requires MV or ECMO</strong></td>
<td>All patients</td>
<td>Dexamethasone should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): * <strong>PO baricitinib</strong>(^i) (BII) * <strong>IV tocilizumab</strong>(^i) (BII) Add remdesivir to 1 of the options above in certain patients (for examples, see footnote).(^j)</td>
</tr>
</tbody>
</table>

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See [Guidelines Development](https://www.covid19treatmentguidelines.nih.gov/) for more information.
For a list of risk factors, see the CDC webpage [Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19](https://www.cdc.gov/coronavirus/2019-ncov/healthcare-professionals/underlying-conditions.html).

Ritonavir-boosted nirmatrelvir (Paxlovid) has not been studied in hospitalized patients. The FDA EUA for ritonavir-boosted nirmatrelvir allows for its use in hospitalized patients with mild to moderate COVID-19 (i.e., those who do not require supplemental oxygen) who are at high risk of progressing to severe COVID-19 and who are within 5 days of symptom onset.

Corticosteroids that are prescribed for an underlying condition should be continued.

Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset).

Conventional oxygen refers to oxygen supplementation that is not HFNC oxygen, NIV, MV, or ECMO.

If these patients progress to requiring HFNC oxygen, NIV, MV, or ECMO, the full course of remdesivir should still be completed.

If PO baricitinib and IV tocilizumab are not available or not feasible to use, **PO tofacitinib** can be used instead of PO baricitinib (**BIIa**), and **IV sarilumab** can be used instead of IV tocilizumab (**BIIa**).

Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count <50 x 10^9/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder.

If baricitinib or tocilizumab are not readily available, start dexamethasone while waiting for the additional immunomodulator to be acquired. If other immunomodulators cannot be obtained or are contraindicated, use dexamethasone alone.

Examples of patients who may benefit most from adding remdesivir include patients who are immunocompromised (**BIII**); patients with evidence of ongoing viral replication (e.g., those with a low Ct value, as measured by an RT-PCR result or with a positive rapid antigen test result) (**BIIa**); or patients who are ≤10 days from symptom onset (**CIIa**). For more information on immunocompromising conditions, see [Special Considerations in People Who Are Immunocompromised](https://www.covid19treatmentguidelines.nih.gov/).

**Key:** CDC = Centers for Disease Control and Prevention; Ct = cycle threshold; ECMO = extracorporeal membrane oxygenation; ED = emergency department; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; HFNC = high-flow nasal cannula; Hgb = hemoglobin; ICU = intensive care unit; IV = intravenous; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PO = oral; RT-PCR = reverse transcription polymerase chain reaction; ULN = upper limit of normal

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease is driven by a dysregulated immune/inflammatory response to SARS-CoV-2 infection that may lead to further tissue damage and thrombosis. Based on this understanding, therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease, whereas immunosuppressive, anti-inflammatory, and antithrombotic therapies are likely to be more beneficial after COVID-19 has progressed to stages characterized by hypoxemia and endothelial dysfunction.

Currently, most people in the United States have some degree of immunity to SARS-CoV-2 due to COVID-19 vaccination or SARS-CoV-2 infection. The increase in population immunity and the change in variants have led to a decrease in the rate of severe disease caused by COVID-19. Because other co-existing disease processes can cause hypoxemia in patients who test positive for SARS-CoV-2 infection, clinicians should perform the appropriate evaluations to rule out alternative diagnoses.

Below is a summary of the rationale for the COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations on the therapeutic management of hospitalized patients with COVID-19. For dosing information for each of the recommended drugs, please refer to Table 2c below. For more information about these therapies and the evidence that supports the Panel’s recommendations, please refer to the specific drug pages and clinical data tables.

**Patients Who Are Hospitalized for Reasons Other Than COVID-19 and Who Do Not Require Supplemental Oxygen**

Hospitalized patients with COVID-19 who do not require supplemental oxygen are a heterogeneous population. Some patients may be hospitalized for reasons other than COVID-19 but may also have mild...
to moderate COVID-19 (see Clinical Spectrum of SARS-CoV-2 Infection). In these cases, patients who are at high risk of progressing to severe COVID-19 may benefit from antiviral therapy.

Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in adult and pediatric patients aged ≥12 years and weighing ≥40 kg who:

- Are hospitalized; or
- Are not hospitalized, have mild to moderate COVID-19, and are at high risk of progressing to severe COVID-19.

Several other therapies, including ritonavir-boosted nirmatrelvir and molnupiravir, have received FDA Emergency Use Authorizations for use in patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. These therapies can be used in hospitalized patients who qualify for therapy if they were admitted to the hospital for a diagnosis other than COVID-19. The Panel’s recommendations for these patients are the same as those for nonhospitalized patients (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Patients Who Are Hospitalized for COVID-19 and Who Do Not Require Supplemental Oxygen

**Recommendations**

- The Panel recommends using remdesivir for the treatment of COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe disease (BIII).
- Remdesivir should be administered for 5 days or until hospital discharge, whichever comes first.

The rationale for using remdesivir in this population is based on several lines of evidence. In a trial conducted predominantly among hospitalized patients with COVID-19 who were not receiving supplemental oxygen at enrollment, a 5-day course of remdesivir was associated with greater clinical improvement when compared with standard of care. Evidence from the PINETREE trial also suggests that early therapy reduces the risk of progression, although that study was performed in high-risk, unvaccinated, nonhospitalized patients with ≤7 days of symptoms who received a 3-day course of remdesivir.

Other studies have not shown a clinical benefit of remdesivir in this group of hospitalized patients with COVID-19. In the ACTT-1 trial, remdesivir showed no significant benefit in hospitalized patients with mild to moderate disease; however, only 13% of the study population did not require supplemental oxygen. In the large Solidarity trial, the use of remdesivir was not associated with a survival benefit among the subset of hospitalized patients who did not require supplemental oxygen. See Table 4a for more information.

The aggregate data on using remdesivir to treat this population show a faster time to recovery in patients who received remdesivir but no clear evidence of a survival benefit. Because remdesivir has been shown to reduce the risk of disease progression, the Panel recommends using remdesivir in hospitalized patients with COVID-19 who are at risk of progressing to severe disease. For information on medical conditions that confer high risk, see the Centers for Disease Control and Prevention webpage People With Certain Medical Conditions.

**Recommendation**

- The Panel recommends against the use of dexamethasone (AIIa) or other systemic corticosteroids (AIII) for the treatment of COVID-19 in patients who do not require supplemental oxygen.

In the RECOVERY trial, no survival benefit was observed for dexamethasone among the subset of
patients with COVID-19 who did not require supplemental oxygen at enrollment.\(^4\) In an observational cohort study of U.S. veterans, the use of dexamethasone was associated with higher mortality in hospitalized patients with COVID-19 who did not require supplemental oxygen.\(^5\)

There are insufficient data to inform the use of other systemic corticosteroids in hospitalized patients with COVID-19. Patients who are receiving corticosteroid treatment for an underlying condition should continue to receive corticosteroids. See Table 5a for more information.

**Patients Who Require Conventional Oxygen**

Patients with COVID-19 who require conventional oxygen (i.e., those who do not require high-flow nasal cannula [HFNC] oxygen, noninvasive ventilation [NIV], or mechanical ventilation) are a heterogeneous population. Although the oxygen requirement qualifies all these patients as having severe disease, some of these patients will improve after a short period with or without treatment; others will develop progressive disease. There is no consensus on which clinical or laboratory parameters should be used to determine a patient’s risk of progression and guide therapy.

**Recommendation**

- For patients with COVID-19 who only require minimal conventional oxygen, the Panel recommends using remdesivir without dexamethasone (BIIa).

In these patients, the hyperinflammatory state for which corticosteroids might be most beneficial may not yet be present or fully developed. In a subgroup analysis during the ACTT-1 trial, remdesivir significantly reduced the time to clinical recovery and significantly reduced mortality among the subset of patients who were receiving conventional oxygen at enrollment.\(^2\) Evidence from ACTT-1 and a pooled analysis of individual data from 9 randomized controlled trials\(^6\) suggest that remdesivir will have its greatest benefit when administered early in the clinical course of COVID-19 (e.g., within 10 days of symptom onset). See Table 4a for more information.

**Recommendations**

- For most patients with COVID-19 who require conventional oxygen, the Panel recommends using dexamethasone plus remdesivir (BIIa).
- If dexamethasone is not available, an equivalent dose of another corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) may be used (BIII).

The results of several studies suggest that the use of remdesivir plus dexamethasone improves clinical outcomes among hospitalized patients with COVID-19. In the CATCO trial, in which 87% of patients received corticosteroids and 54% were on conventional oxygen, remdesivir significantly reduced the need for mechanical ventilation among the subset of patients who did not require mechanical ventilation at enrollment when compared with standard of care.\(^7\) In the Solidarity trial, in which approximately two-thirds of the patients received corticosteroids, remdesivir significantly reduced mortality among the subset of patients who were receiving conventional or HFNC oxygen at enrollment.\(^3\) See Table 4a for more information.

An individual patient-level meta-analysis of 8 clinical trials examined the efficacy of using remdesivir in hospitalized patients with COVID-19.\(^6\) This meta-analysis found that remdesivir significantly reduced the number of patients who required mechanical ventilation or who died by Day 28 in the combined subgroups of patients who did not require oxygen or who were receiving conventional oxygen at baseline. However, the effect of remdesivir was not evaluated in the subgroup of patients who were receiving conventional oxygen at enrollment.
Recommendation

- If remdesivir is not available, the Panel recommends using dexamethasone alone in patients with COVID-19 who require conventional oxygen (BII).

In the RECOVERY trial, dexamethasone significantly reduced mortality among the subset of patients who were receiving oxygen (defined as receiving oxygen supplementation but not mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) at enrollment.4 Remdesivir was administered to <1% of the study participants. Results for patients who were only receiving conventional oxygen at enrollment were not available. See Table 5a for more information.

Recommendation

- For patients with COVID-19 who have rapidly increasing oxygen needs and systemic inflammation, the Panel recommends adding a second immunomodulatory drug, such as oral (PO) baricitinib (BIIa) or intravenous (IV) tocilizumab (BIIa), to dexamethasone.

Several large randomized trials have evaluated the use of dexamethasone in combination with a second immunomodulator, including baricitinib (a Janus kinase [JAK] inhibitor)\textsuperscript{8-10} and tocilizumab (an interleukin [IL]-6 inhibitor).\textsuperscript{11-13} These studies included some patients who required conventional oxygen only, as well as those with increasing oxygen needs and/or elevated levels of inflammatory markers. Subgroup analyses in these trials have not clearly defined which patients in this heterogeneous group are most likely to benefit from adding another immunomodulator to their corticosteroid regimens. Nonetheless, some trials suggest that adding a second immunomodulator to dexamethasone provides benefits to patients who require conventional oxygen, especially those with rapidly increasing oxygen requirements and systemic inflammation.

The Panel does not have a preference for using baricitinib or tocilizumab in this group of patients. The strength of the evidence for these agents is similar, and there are no studies that directly compare the use of these agents as treatments for COVID-19.

Use of Anticoagulants

- The Panel recommends using a therapeutic dose of heparin for nonpregnant patients with D-dimer levels above the upper limit of normal who require conventional oxygen and who do not have an increased bleeding risk (CIIa).

- Patients who do not meet the criteria for therapeutic heparin noted above, including pregnant individuals, should receive a prophylactic dose of heparin unless this drug is contraindicated (AI); (BIII) for pregnant patients.

The Panel’s recommendations for the use of heparin are based on data from 3 open-label randomized controlled trials that compared the use of therapeutic doses of heparin to prophylactic or intermediate doses of heparin in hospitalized patients who did not require intensive care unit (ICU)-level care. Pooled data from the ATTACC/ACTIV-4a/REMAP-CAP trials reported more organ support-free days for patients in the therapeutic heparin arm than in the usual care arm, but there was no difference between the arms in mortality or length of hospitalization.\textsuperscript{14} The RAPID trial compared a therapeutic dose of heparin to a prophylactic dose in hospitalized patients with moderate COVID-19. There was no statistically significant difference between the arms in the occurrence of the primary endpoint (which was a composite endpoint of ICU admission and initiation of NIV or mechanical ventilation), but the therapeutic dose of heparin reduced 28-day mortality.\textsuperscript{15} In the HEP-COVID trial, venous thromboembolism (VTE), arterial thromboembolism, and death by Day 30 occurred significantly less frequently in patients who received a therapeutic dose of heparin than in those who received a prophylactic dose of heparin, but there was no difference in mortality by Day 30 between the arms.\textsuperscript{16}
Patients Who Require High-Flow Nasal Cannula Oxygen or Noninvasive Ventilation

In these patients, systemic inflammation contributes to hypoxemia, and thus these patients benefit from receiving a second immunomodulator in addition to dexamethasone. There is no consensus on which clinical or laboratory parameters reliably predict the risk of death or progression to mechanical ventilation.

The available evidence suggests that the benefits of adding baricitinib or tocilizumab to dexamethasone treatment outweigh the potential risks in patients with COVID-19 who require HFNC oxygen or NIV. Although the combination of dexamethasone and secondary immunomodulating medications may increase the risk of opportunistic infections or the risk of reactivating latent infections, there are insufficient data to make recommendations about initiating prophylaxis against these infections.

Recommendations

- **Dexamethasone** should be administered to all patients with COVID-19 who require HFNC oxygen or NIV (AI).
  - If the patient has not already received a second immunomodulator in addition to dexamethasone, promptly add 1 of the following (listed in order of preference):
    - **PO baricitinib** (AI)
    - **IV tocilizumab** (BIIa)

Dexamethasone should be initiated immediately, without waiting until the second immunomodulator can be acquired. Dexamethasone was used as a single-agent immunomodulatory strategy in the RECOVERY trial and demonstrated a survival benefit among patients who required supplemental oxygen. In this trial, the treatment effect for dexamethasone could not be evaluated separately for those who required conventional oxygen and those who required HFNC oxygen or NIV (see **Systemic Corticosteroids**).

Several large randomized controlled trials have demonstrated that patients with COVID-19 who require HFNC oxygen or NIV benefit from combining dexamethasone with an additional immunomodulator, such as a JAK inhibitor (e.g., baricitinib, tofacitinib) or an IL-6 inhibitor (e.g., tocilizumab, sarilumab). The quality of the evidence and the totality of the data support a stronger recommendation for baricitinib than for tocilizumab. Every effort should be made to obtain baricitinib or tocilizumab.

Two large randomized controlled trials (the RECOVERY and COV-BARRIER trials) both reported a survival benefit among hospitalized patients with COVID-19 who required HFNC oxygen or NIV and who received baricitinib plus dexamethasone. Data from the ACTT-2 and ACTT-4 trials support the overall safety of using baricitinib in combination with remdesivir and the potential for a clinical benefit of this combination, but neither trial studied baricitinib in combination with dexamethasone as the standard of care.

The use of tocilizumab in combination with corticosteroids reduced in-hospital mortality in patients with rapid respiratory decompensation who were admitted to the ICU in the REMAP-CAP trial. Similar results were reported during the RECOVERY trial. However, patients were only selected for randomization into the tocilizumab arm during the RECOVERY trial if they had oxygen saturation <92% on room air and C-reactive protein levels ≥75 mg/L. These factors put them at higher risk of clinical progression. Both REMAP-CAP and RECOVERY evaluated the efficacy of adding tocilizumab to standard care; in both cases, standard care included dexamethasone therapy. Other randomized trials that have evaluated the use of tocilizumab have demonstrated mixed results, including a lack of benefit when tocilizumab was administered without dexamethasone as part of standard care.

Combinations of 3 immunomodulators (e.g., dexamethasone plus baricitinib plus tocilizumab) have not been studied in clinical trials. Although some patients in the baricitinib arm of the RECOVERY trial also
received tocilizumab, data from the study are insufficient to issue a recommendation. When both agents are used, there is a potential for additive risk of secondary infections.\textsuperscript{10}

The clinical trial data cited above informed the Panel’s recommendations for adding a second immunomodulator to dexamethasone in hospitalized patients who require HFNC oxygen or NIV. Based on these clinical trial results, the Panel recommends baricitinib over tocilizumab as the second immunomodulator. See Table 5c and Table 5d for more information.

**Recommendation**

- If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib (BIIa), and IV sarilumab can be used instead of IV tocilizumab (BIIa).

If neither baricitinib nor tocilizumab is available or feasible to use, the JAK inhibitor tofacitinib or the IL-6 inhibitor sarilumab may be used as alternative agents for baricitinib or tocilizumab, respectively. Tofacitinib decreased the risk of respiratory failure or death in the STOP-COVID trial,\textsuperscript{22} and sarilumab reduced mortality and the duration of organ support to the same degree as tocilizumab in the REMAP-CAP trial.\textsuperscript{13}

**Recommendations**

- For certain hospitalized patients who require HFNC oxygen or NIV, the Panel recommends adding remdesivir to 1 of the recommended immunomodulator combinations. Examples of patients who may benefit most from adding remdesivir include:
  - Patients who are immunocompromised (BIII)
  - Patients with evidence of ongoing viral replication (e.g., those with a low cycle threshold [Ct] value, as measured by a reverse transcription polymerase chain reaction [RT-PCR] result or with a positive rapid antigen test result) (BIII)
  - Patients who are ≤10 days from symptom onset (CIIa)

Clinical trial data have not clearly established that remdesivir reduces the time to recovery or improves survival in patients who require HFNC oxygen or NIV. However, because clinical trials have found that remdesivir prevents clinical progression in patients who are not on mechanical ventilation, some patients receiving HFNC oxygen or NIV might benefit from receiving remdesivir. In the Solidarity trial, remdesivir had a modest but statistically significant effect on reducing the risk of death or progression to ventilation in patients who were receiving oxygen but who were not ventilated at baseline.\textsuperscript{3} However, these effects could not be evaluated separately for patients who required conventional oxygen supplementation and those who required HFNC oxygen or NIV.\textsuperscript{3} Among the patients who were not receiving mechanical ventilation at baseline during the CATCO trial, 8% of patients who received remdesivir required mechanical ventilation compared to 15% of those who received standard of care (relative risk 0.53; 95% CI, 0.38–0.75).\textsuperscript{7} See Table 4a for more information.

The Panel’s rationale for recommending remdesivir for certain patients who require HFNC oxygen or NIV is discussed below. This discussion includes examples of patients who may benefit most from receiving remdesivir. In addition, clinicians may extend the course of remdesivir beyond 5 days in this population based on clinical response.

**Patients Who Are Immunocompromised**

People who are immunocompromised already have difficulty achieving viral clearance. The use of immunomodulators to treat COVID-19 may further impair this process. Because SARS-CoV-2
replication may be prolonged in these patients, remdesivir may help enhance viral clearance and improve outcomes. In a large, retrospective study of a cohort of patients who were immunocompromised, patients who received remdesivir had a lower risk of mortality than those who did not receive remdesivir; however, only 19% of the patients in the study were receiving HFNC oxygen or NIV. For more information, see Special Considerations in People Who Are Immunocompromised.

**Patients With Suspected Ongoing Viral Replication**

Hospitalized patients who require HFNC oxygen or NIV are routinely treated with 2 immunomodulators to prevent or mitigate inflammatory-mediated injury. These treatments may impair the patient’s ability to achieve viral clearance; thus, directly treating the virus with remdesivir may theoretically help improve outcomes. Substantial evidence from studies of other viral diseases supports the benefits of reducing the viral burden. Ct values can be obtained from some SARS-CoV-2 RT-PCR assays, and these values may be used as a proxy for the level of ongoing viral replication (low Ct values correspond to higher viral loads). While this information is not available on all RT-PCR platforms, Ct values may be helpful in informing decisions regarding the use of remdesivir. Positive rapid antigen test results are also consistent with higher viral loads.

**Patients Who Are Within 10 Days of Symptom Onset**

Active viral replication occurs early in the course of SARS-CoV-2 infection. Evidence from the ACTT-1 and PINETREE trials suggests that remdesivir will have the greatest benefit when administered early in the clinical course of COVID-19. In the ACTT-1 trial, remdesivir demonstrated a greater benefit in patients who were enrolled within 10 days of symptom onset than in those who were enrolled later in the disease course.

**Use of Anticoagulants**

- For patients without an indication for therapeutic anticoagulation, the Panel recommends using a prophylactic dose of heparin as VTE prophylaxis, unless a contraindication exists (AI); (BIII) for pregnant patients.
- For patients who are started on a therapeutic dose of heparin in a non-ICU setting for the management of COVID-19 and then transferred to the ICU, the Panel recommends switching from the therapeutic dose to a prophylactic dose of heparin, unless VTE is confirmed (BIII).
- The Panel recommends against the use of an intermediate dose (e.g., enoxaparin 1 mg/kg once daily) or a therapeutic dose of anticoagulation for VTE prophylaxis, except in a clinical trial (BI).

The INSPIRATION trial compared the use of intermediate doses of anticoagulation to prophylactic doses in adults who were admitted to the ICU with COVID-19. There was no difference between the arms in the incidence of VTE, the incidence of arterial thrombosis, the need for ECMO, or all-cause mortality. The multiplatform randomized controlled trial REMAP-CAP/ACTIV-4a/ATTACC compared the effectiveness of a therapeutic dose of heparin to standard care in critically ill patients with COVID-19. The study did not show an increase in the number of organ support-free days or the probability of survival to hospital discharge among patients who received therapeutic doses of anticoagulation. See Antithrombotic Therapy in Patients With COVID-19 for more information.

**Patients Who Require Mechanical Ventilation or Extracorporeal Membrane Oxygenation**

**Recommendations**

- Dexamethasone should be administered to all patients with COVID-19 who require mechanical ventilation or ECMO (AI).
- If the patient has not already received a second immunomodulator in addition to dexamethasone, promptly add 1 of the following (listed in alphabetical order):
  - PO baricitinib (BIIa)
• IV tocilizumab (BIIa)

Dexamethasone was shown to reduce mortality in critically ill patients with COVID-19 in a meta-analysis that aggregated 7 randomized trials and included data on 1,703 critically ill patients. The largest trial included in the meta-analysis was the RECOVERY trial, which had a subgroup of patients who were receiving mechanical ventilation (see Systemic Corticosteroids and Table 5a).⁴ Subsequent studies of immunomodulator therapy suggest that using a second immunomodulator in combination with dexamethasone is more effective in patients with COVID-19 who require mechanical ventilation or ECMO.

Clinical trials that have evaluated combining IL-6 inhibitors or JAK inhibitors with corticosteroids for the treatment of patients with COVID-19 provide the most robust evidence for the Panel’s recommendations.

Clinical trials of tocilizumab have reported an overall survival benefit in patients with hypoxemia and signs of systemic inflammation (RECOVERY)¹¹ and in patients who are critically ill and require organ support (REMAP-CAP).¹² Although these studies included patients who were receiving mechanical ventilation at randomization, the studies were not specifically powered to assess the effectiveness of IL-6 inhibitors in these patients. Other studies of tocilizumab in critically ill patients did not find a survival benefit, although the time between initiation of organ support in the ICU and study enrollment differed across the studies (see Table 5c).¹⁸,²¹ The use of corticosteroids also varied across the studies.

An extension of the COV-BARRIER trial compared the efficacy of baricitinib to placebo in 101 critically ill patients with COVID-19. The study reported significant reductions in mortality (relative reduction of 46% at 28 days and 44% at 60 days) and no major adverse events among patients who received baricitinib.²⁸ Systematic reviews of JAK inhibitors confirm the efficacy of using baricitinib in hospitalized patients with COVID-19 who require oxygen support. There is a lower certainty of evidence for patients who were receiving mechanical ventilation or ECMO, and baricitinib may have modestly attenuated efficacy in this group.²⁹ Baricitinib or tocilizumab should only be administered in combination with dexamethasone or another corticosteroid.

For guidance regarding the use of tofacitinib and sarilumab if baricitinib and tocilizumab are not available or feasible to use, please refer to the rationale for patients who require HFNC oxygen or NIV.

**Considerations for the Use of Remdesivir**

Remdesivir is most effective against COVID-19 in patients who are earlier in the course of the disease and who do not require mechanical ventilation or ECMO. Among patients who were receiving mechanical ventilation or ECMO during the Solidarity trial, there was a trend toward an increase in mortality for patients treated with remdesivir.³ For patients who progress to requiring mechanical ventilation or ECMO after they initiate remdesivir, the Panel suggests continuing remdesivir until the treatment course is completed.

Subgroup analyses from 2 randomized trials suggest there is no clinical benefit to using a combination of remdesivir and dexamethasone in patients who are receiving mechanical ventilation or ECMO.⁷,¹⁷ The data are inconclusive on whether corticosteroid therapy may delay viral clearance in patients with COVID-19.³⁰-³⁴

**Use of Anticoagulants**

- The Panel recommends using a **prophylactic dose of heparin** as VTE prophylaxis, unless a contraindication exists (AI); (BIII) for pregnant patients.

- For patients who are started on a therapeutic dose of heparin in a non-ICU setting for the management of COVID-19 and then transferred to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation (BIII).

- The Panel **recommends against** the use of an **intermediate dose** (e.g., enoxaparin 1 mg/kg daily)
or a **therapeutic dose of anticoagulation** for VTE prophylaxis in critically ill patients with COVID-19, except in a clinical trial (BI).

Patients who required mechanical ventilation or ECMO were included in the multiplatform REMAP-CAP/ACTIV-4a/ATTACC and INSPIRATION trials that studied therapeutic doses and intermediate doses of heparin, respectively.26,27 Because these studies reported no benefits of using intermediate or therapeutic doses of heparin, the recommendations for using prophylactic doses of heparin in hospitalized patients who require mechanical ventilation or ECMO are the same as those for patients who require HFNC oxygen or NIV.

### Table 2c. Dosing Regimens for the Drugs Recommended in Table 2b

The drugs in this table are listed in alphabetical order.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Comments</th>
</tr>
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</table>
| Baricitinib | BAR dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge (whichever comes first). | eGFR ≥60 mL/min/1.73 m²: BAR 4 mg PO once daily  
i.eGR 30 to <60 mL/min/1.73 m²: BAR 2 mg PO once daily  
i.eGR 15 to <30 mL/min/1.73 m²: BAR 1 mg PO once daily  
i.eGR <15 mL/min/1.73 m²: BAR is not recommended. |
| Dexamethasone | DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge (whichever comes first) | If DEX is not available, an equivalent dose of another corticosteroid may be used.  
For more information, see [Systemic Corticosteroids](#). |
| Heparin | Therapeutic dose of SUBQ LMWH or IV UFH | Administer for 14 days or until hospital discharge (whichever comes first) unless there is a diagnosis of VTE or another indication for therapeutic anticoagulation. |
| | Prophylactic dose of SUBQ LMWH or SUBQ UFH | Administer for the duration of the hospital stay. |
| Remdesivir | RDV 200 mg IV once, then RDV 100 mg IV once daily for 4 days or until hospital discharge (whichever comes first) | If the patient is hospitalized for reasons other than COVID-19, the treatment duration is 3 days. For more information, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).  
If the patient progresses to more severe illness, complete the course of RDV. |
| Sarilumab | Use the single-dose, prefilled syringe (not the prefilled pen) for SUBQ injection. Reconstitute sarilumab 400 mg in 100 cc 0.9% NaCl and administer as an IV infusion over 1 hour. | Use if BAR or tocilizumab is not available or not feasible to use (BIIa).  
In the United States, the currently approved route of administration for sarilumab is SUBQ injection. In the REMAP-CAP trial, the SUBQ formulation was used to prepare the IV infusion. |
| Tocilizumab | Tocilizumab 8 mg/kg actual body weight (up to 800 mg) administered as a single IV dose | In clinical trials, a third of the participants received a second dose of tocilizumab 8 hours after the first dose if no clinical improvement was observed. |
| Tofacitinib | Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge (whichever comes first) | Use if BAR or tocilizumab is not available or not feasible to use (BIIa).  
i.eGR <60 mL/min/1.73 m²: tofacitinib 5 mg PO twice daily |

**Key:** BAR = baricitinib; DEX = dexamethasone; eGFR = estimated glomerular filtration rate; IV = intravenous; LMWH = low-molecular-weight heparin; NaCl = sodium chloride; PO = oral; RDV = remdesivir; SUBQ = subcutaneous; UFH = unfractionated heparin; VTE = venous thromboembolism

## References


