Table 2c. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

<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>Hospitalized for Reasons Other Than COVID-19</td>
<td>Recommendations for Antiviral or Immunomodulator Therapy</td>
<td>Recommendations for Anticoagulant Therapy</td>
</tr>
<tr>
<td>Hospitalized but Does Not Require Oxygen Supplementation</td>
<td>Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>See Therapeutic Management of Nonhospitalized Adults With COVID-19.</td>
</tr>
<tr>
<td>Hospitalized and Requires Conventional Oxygen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>All patients</td>
<td>For patients without an indication for therapeutic anticoagulation:</td>
</tr>
<tr>
<td></td>
<td>The Panel recommends against the use of dexamethasone (AIIa) or other systemic corticosteroids (AIII) for the treatment of COVID-19.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>▪ Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients</td>
</tr>
<tr>
<td>Hospitalized and Requires HFNC Oxygen or NIV</td>
<td>Patients who require minimal conventional oxygen</td>
<td>For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk:</td>
</tr>
<tr>
<td></td>
<td>Remdesivir&lt;sup&gt;c&lt;/sup&gt; (BIIa)</td>
<td>▪ Therapeutic dose of heparin&lt;sup&gt;d&lt;/sup&gt; (CIIa)</td>
</tr>
<tr>
<td></td>
<td>Most patients</td>
<td>For other patients:</td>
</tr>
<tr>
<td></td>
<td>Use dexamethasone plus remdesivir&lt;sup&gt;d&lt;/sup&gt; (BIIa). If remdesivir cannot be obtained, use dexamethasone (BII).</td>
<td>▪ Prophylactic dose of heparin&lt;sup&gt;d&lt;/sup&gt; (BIII) for pregnant patients</td>
</tr>
<tr>
<td></td>
<td>Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation</td>
<td>▪ Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients</td>
</tr>
<tr>
<td></td>
<td>Add PO baricitinib&lt;sup&gt;f&lt;/sup&gt; or IV tocilizumab&lt;sup&gt;f&lt;/sup&gt; to 1 of the options above (BIIa).</td>
<td></td>
</tr>
<tr>
<td>Hospitalized and Requires MV or ECMO</td>
<td>Most patients</td>
<td>For patients without an indication for therapeutic anticoagulation:</td>
</tr>
<tr>
<td></td>
<td>Promptly start 1 of the following, if not already initiated:</td>
<td>▪ Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone plus PO baricitinib&lt;sup&gt;f&lt;/sup&gt; (AI)</td>
<td>For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a prophylactic dose of heparin, unless there is another indication for therapeutic anticoagulation (BII).</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone plus IV tocilizumab&lt;sup&gt;f&lt;/sup&gt; (BIIa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone&lt;sup&gt;e&lt;/sup&gt; (AI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Add remdesivir to 1 of the options above in certain patients (CIIa).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Promptly start 1 of the following, if not already initiated:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone plus PO baricitinib&lt;sup&gt;f&lt;/sup&gt; (BIIa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone plus IV tocilizumab&lt;sup&gt;f&lt;/sup&gt; (BIIa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone&lt;sup&gt;e&lt;/sup&gt; (AI)</td>
<td></td>
</tr>
</tbody>
</table>
Rating of Recommendations: A = Strong; B = Moderate; C = Weak
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

a For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19.
b Corticosteroids that are prescribed for an underlying condition should be continued.
c 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).
d Conventional oxygen refers to oxygen supplementation that is not HFNC oxygen, NIV, MV, or ECMO.
e If these patients progress to requiring HFNC oxygen, NIV, MV, or ECMO, the full course of remdesivir should still be completed.
f 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).
g 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.
h If a JAK inhibitor or an anti-IL-6 receptor mAb is not readily available, start dexamethasone while waiting for the additional immunomodulator to be acquired. If neither of the other immunomodulators can be obtained, use dexamethasone alone.
i Clinicians may consider adding remdesivir to 1 of the recommended immunomodulator combinations in patients who require HFNC oxygen or NIV, including immunocompromised patients. The Panel recommends against the use of remdesivir without immunomodulators in these patients (AIIa).

Key: CDC = Centers for Disease Control and Prevention; ECMO = extracorporeal membrane oxygenation; ED = emergency department; HFNC = high-flow nasal cannula; Hgb = hemoglobin; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PO = oral; 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 appears to be also 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.

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 2d below. For detailed information regarding the therapies and evidence from clinical trials that support 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 has been 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, and several other therapies 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.

Other studies have not shown a clinical benefit of remdesivir in this group of hospitalized patients with COVID-19. In ACTT-1, 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. Given the impact on reducing progression, the Panel finds that the available data support a recommendation for 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. 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.

There are no data to support the use of other systemic corticosteroids in hospitalized patients with COVID-19. However, patients who are receiving corticosteroid treatment for an underlying condition should continue to receive corticosteroids. See Table 6a 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 ACTTT-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. Evidence from ACTTT-1 suggests 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, or 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. 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. See Table 4a for more information.

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. 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 6a for more information.

Recommendation

• The Panel recommends adding a second immunomodulatory drug (e.g., baricitinib or tocilizumab) to dexamethasone in patients who have rapidly increasing oxygen needs and systemic inflammation (BIIa).
Several large randomized trials evaluated the use of interleukin (IL)-6 inhibitors (e.g., tocilizumab, sarilumab) or Janus kinase (JAK) inhibitors (e.g., baricitinib, tofacitinib) with or without corticosteroids in patients with COVID-19. 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. Because there are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend 1 drug over the other.

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. The multiplatform ATTACC/ACTIV-4a/REMAP-CAP trial 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.12 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.13 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.14

Patients Who Require High-Flow Nasal Cannula Oxygen or Noninvasive Ventilation

In these patients, systemic inflammation contributes to hypoxemia as the predominant clinical feature, and patients benefit from 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, NIV, mechanical ventilation, or ECMO. 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

- For most patients, the Panel recommends using 1 of the following combinations of immunomodulators:
  - **Dexamethasone plus oral (PO) baricitinib (AI); or**
  - **Dexamethasone plus intravenous (IV) tocilizumab (BIIa)**

Several large randomized controlled trials have demonstrated that these patients benefit from combining dexamethasone with an additional immunomodulator, such as an IL-6 inhibitor (e.g., tocilizumab, sarilumab) or a JAK inhibitor (e.g., baricitinib, tofacitinib). See Table 6c and Table 6d for more information.

The use of baricitinib plus dexamethasone was associated with a survival benefit among hospitalized patients with COVID-19 in the RECOVERY trial. The treatment effect was most pronounced among patients who were receiving HFNC oxygen or NIV.\(^{11}\) The COV-BARRIER trial also demonstrated a survival benefit of baricitinib that was most pronounced among patients who were receiving HFNC oxygen or NIV.\(^{10}\) Data from the ACTT-2\(^{9}\) and ACTT-4\(^{15}\) trials support the overall safety of baricitinib and the potential for a clinical benefit, but neither trial studied baricitinib in combination with dexamethasone as the standard of care.

In the REMAP-CAP trial, the use of tocilizumab in combination with corticosteroids reduced in-hospital mortality in patients with rapid respiratory decompensation who were admitted to the ICU.\(^{16}\) Similar results were reported during the RECOVERY trial.\(^{7}\) 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, a potential for additive risk of secondary infections remains.\(^{11}\)

In summary, the clinical trials data cited above informed the Panel’s recommendations for adding a second immunomodulator to dexamethasone in hospitalized patients who require HFNC oxygen or NIV. The quality of the evidence and the totality of the data support a stronger recommendation for baricitinib than tocilizumab. See Table 6c and Table 6d 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).

When 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 for respiratory failure or death in the STOP-COVID trial,\(^ {17}\) and sarilumab reduced mortality and the duration of organ support to the same degree as tocilizumab in the REMAP-CAP trial.\(^ {8}\)
**Recommendation**

- The Panel recommends using **dexamethasone alone** if baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained (AII).

Significant effort should be made to obtain baricitinib, tofacitinib, tocilizumab, or sarilumab. 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. At the time of the 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 **Corticosteroids**).

**Recommendation**

- For hospitalized patients who require HFNC oxygen or NIV and have certain medical conditions, the Panel recommends adding **remdesivir** to 1 of the recommended immunomodulator combinations (CIIa).

Although clinical trial data have not established a clear benefit of using remdesivir in patients who require HFNC oxygen or NIV, the Panel’s recommendation reflects the balance of 2 factors. First, given that these patients are routinely treated with 2 immunomodulators to prevent or mitigate inflammatory-mediated injury, these treatments may impair the patient’s antiviral response, and directly treating the virus with remdesivir may help improve outcomes. In this context, some Panel members would add remdesivir to treatments for immunocompromised patients who require HFNC oxygen or NIV. In addition, clinicians may extend the course of remdesivir beyond 5 days in this population based on clinical response. In the Solidarity trial, remdesivir had a modest but statistically significant effect on reducing the risk of death or progression to mechanical ventilation; however, these effects could not be evaluated separately for patients who required conventional oxygen supplementation and those who required HFNC oxygen or NIV. See Table 4a for more information.

**Recommendation**

- The Panel **recommends against** the use of remdesivir without immunomodulators in hospitalized patients who require HFNC oxygen or NIV (AIIa).

In the ACTT-1 trial, hospitalized patients with COVID-19 received remdesivir or placebo without immunomodulators. In the subgroup of 193 patients who required high-flow oxygen or NIV at enrollment, there was no difference in time to recovery between patients in the remdesivir arm and patients in the placebo arm (recovery rate ratio 1.09; 95% CI, 0.76–1.57). A post hoc analysis did not show a survival benefit for remdesivir at Day 29 (HR 1.02; 95% CI, 0.54–1.91).

The Panel recommends against using remdesivir without immunomodulators in patients who require HFNC oxygen or NIV because there is uncertainty regarding whether using remdesivir by itself confers a clinical benefit in this subgroup. Patients who are taking remdesivir and then progress to requiring HFNC oxygen or NIV should complete the course of remdesivir. If these patients are not already receiving 1 of the recommended immunomodulator combinations as part of their treatment, they should initiate immunomodulatory therapy.

**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 (BII).

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

Recommendation

• The Panel recommends initiating dexamethasone plus PO baricitinib (BIIa) or dexamethasone plus IV tocilizumab (BIIa) if not already initiated in patients with COVID-19 who require mechanical ventilation or ECMO.

Clinical trials that have evaluated combining IL-6 inhibitors and 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) and in patients who are critically ill and require organ support (REMAP-CAP). 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 6c). 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. 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. Baricitinib or tocilizumab should only be administered in combination with dexamethasone or another corticosteroid.

Regarding the use of tocilizumab 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.

Recommendation

• The Panel recommends using dexamethasone alone for the treatment of patients with COVID-19.
who require mechanical ventilation or ECMO if baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained (AI).

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 in the meta-analysis was the RECOVERY trial, which included a subgroup of patients who were receiving mechanical ventilation (see Corticosteroids and Table 6a). However, as noted above, subsequent studies of immunomodulator therapy suggest that using a combination of dexamethasone and another immunomodulator is more effective in patients with COVID-19 who require mechanical ventilation or ECMO.

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. However, in the Solidarity trial, among patients who were receiving mechanical ventilation or ECMO, there was a trend toward an increase in mortality for patients treated with remdesivir. For patients who started on remdesivir and progressed to requiring mechanical ventilation or ECMO, 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. The data are inconclusive on whether corticosteroid therapy may delay viral clearance in patients with COVID-19. Given the conflicting results from observational studies and the lack of clinical trial data, some Panel members would add remdesivir to dexamethasone and a second immunomodulator only in patients who have recently been placed on mechanical ventilation.

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) and 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. Because these studies reported no benefits to 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 2d. Dosing Regimens for the Drugs Recommended in Table 2c

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>
</thead>
</table>
| Baricitinib   | BAR dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge (whichever comes first). | • eGFR $\geq$60 mL/min/1.73 m$^2$: BAR 4 mg PO once daily  
• eGFR 30 to $<$60 mL/min/1.73 m$^2$: BAR 2 mg PO once daily  
• eGFR 15 to $<$30 mL/min/1.73 m$^2$: BAR 1 mg PO once daily  
• eGFR $<$15 mL/min/1.73 m$^2$: 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 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                                     |                                                                                                    |
| 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 (see Therapeutic Management of Nonhospitalized Adults With COVID-19).  
• If the patient progresses to more severe illness, complete the course of RDV.  
• For a discussion on using RDV in patients with renal insufficiency, see Remdesivir. |
| 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).  
• eGFR $<60$ mL/min/1.73 m$^2$: 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


