

## 6: Therapeutic Management of Patients With COVID-19

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*Last Updated: May 24, 2021*

### Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

No therapy has been proven to be beneficial in outpatients with mild to moderate COVID-19 who are not at high risk for disease progression. The COVID-19 Treatment Guidelines Panel (the Panel) recommends providing supportive care and symptomatic management to outpatients with COVID-19; steps should also be taken to reduce the risk of SARS-CoV-2 transmission to others.<sup>1,2</sup> Patients should be advised about when to seek in-person evaluation. See [Outpatient Management of Acute COVID-19](#) for more information.

In outpatients with mild to moderate COVID-19 who are at high risk for disease progression, anti-SARS-CoV-2 antibody-based therapies may have the greatest potential for clinical benefit during the earliest stages of infection. For these patients, the Panel recommends administering **bamlanivimab plus etesevimab (AIIa)** or **casirivimab plus imdevimab (AIIa)**, both of which are available through Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA). See [Anti-SARS-CoV-2 Monoclonal Antibodies](#) for more information about using these combinations and other monoclonal antibodies.

Remdesivir, an antiviral agent, is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.<sup>3-6</sup>

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest benefit observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this setting.<sup>7-10</sup>

Adding tocilizumab, a recombinant humanized anti-interleukin-6 receptor monoclonal antibody, to dexamethasone therapy was found to improve survival among patients who were exhibiting rapid respiratory decompensation due to COVID-19.<sup>11,12</sup>

The Panel continues to review the most recent clinical data to provide up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19. Figure 1 summarizes the Panel's recommendations for managing patients with varying severities of disease.

## Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnotes.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	<p>For patients who are not at high risk for disease progression, provide supportive care and symptomatic management <b>(AIII)</b>.</p> <p>For patients who are at high risk of disease progression (as defined by the FDA EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies), use one of the following combinations:</p> <ul style="list-style-type: none"> <li>• <b>Bamlanivimab plus etesevimab (AIIa)</b></li> <li>• <b>Casirivimab plus imdevimab (AIIa)</b></li> </ul>
Hospitalized but Does Not Require Supplemental Oxygen	<p>There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.</p>
Hospitalized and Requires Supplemental Oxygen	<p>Use one of the following options:</p> <ul style="list-style-type: none"> <li>• <b>Remdesivir<sup>a,b</sup></b> (e.g., for patients who require minimal supplemental oxygen) <b>(BIIa)</b></li> <li>• <b>Dexamethasone<sup>c</sup> plus remdesivir<sup>a,b</sup></b> (e.g., for patients who require increasing amounts of supplemental oxygen) <b>(BIII)<sup>d,e</sup></b></li> <li>• <b>Dexamethasone<sup>c</sup></b> (e.g., when combination therapy with remdesivir cannot be used or is not available) <b>(BI)</b></li> </ul>
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	<p>Use one of the following options:</p> <ul style="list-style-type: none"> <li>• <b>Dexamethasone<sup>c</sup> (AI)<sup>e</sup></b></li> <li>• <b>Dexamethasone<sup>c</sup> plus remdesivir<sup>a,b</sup> (BIII)<sup>d,e</sup></b></li> </ul> <p>For patients who were recently hospitalized<sup>f</sup> with rapidly increasing oxygen needs and systemic inflammation:</p> <ul style="list-style-type: none"> <li>• Add <b>tocilizumab<sup>g</sup></b> to one of the two options above <b>(BIIa)</b></li> </ul>
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	<ul style="list-style-type: none"> <li>• <b>Dexamethasone<sup>c</sup> (AI)<sup>h</sup></b></li> </ul> <p>For patients who are within 24 hours of admission to the ICU:</p> <ul style="list-style-type: none"> <li>• <b>Dexamethasone<sup>c</sup> plus tocilizumab<sup>g</sup> (BIIa)</b></li> </ul>

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**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

<sup>a</sup> The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.

<sup>b</sup> For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.

<sup>c</sup> The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.

<sup>d</sup> The combination of dexamethasone and remdesivir has not been studied in clinical trials.

<sup>e</sup> In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.

<sup>f</sup> For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.

<sup>g</sup> The tocilizumab dose is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. Tocilizumab should not be combined with baricitinib and should be avoided in certain groups of patients who are at increased risk for complications. See the Interleukin-6 Inhibitors section for more information.

<sup>h</sup> The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of remdesivir monotherapy in these patients.

**Key:** ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; ICU = intensive care unit; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

For definitions of the clinical severity categories for patients with COVID-19, please see [Clinical Spectrum of SARS-CoV-2 Infection](#).

## Patients With Mild to Moderate COVID-19 Who Are Not Hospitalized

### *Recommendations*

For patients who are not at high risk of disease progression:

- The Panel recommends providing supportive care and symptomatic management (**AIII**).

For patients who are at high risk of disease progression, as defined by the EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies:

- The Panel recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies (treatments are listed in alphabetical order):
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or**
  - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).**
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or a nucleic acid amplification test and within 10 days of symptom onset.

### *Additional Considerations*

- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab.
  - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K, that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
  - The availability of bamlanivimab plus etesevimab may be restricted in areas with an elevated prevalence of variants of concern that have markedly reduced in vitro susceptibility to these agents (e.g., P.1, B.1.351). Please visit [this website](#) from the Department of Health and Human Services for updates on the distribution of bamlanivimab plus etesevimab and the [Centers for Disease Control and Prevention's website](#) for information on the proportions of SARS-CoV-2 variants.
  - In regions where SARS-CoV-2 variants of concern or interest with modestly reduced in vitro susceptibility to bamlanivimab plus etesevimab are common (e.g., B.1.526), some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.

### *Rationale for Recommending Supportive Care and Symptomatic Management for Patients Who Are Not at High Risk of Disease Progression*

No specific therapy has been proven to be beneficial in outpatients with mild to moderate COVID-19 who are not at high risk for disease progression. The Panel recommends supportive care and symptomatic management (**AIII**), with close monitoring for worsening symptoms and clinical deterioration for patients.

### *Rationale for the Use of Combination Anti-SARS-CoV-2 Monoclonal Antibodies*

Two anti-SARS-CoV-2 combination products—bamlanivimab plus etesevimab and casirivimab plus imdevimab—have received EUAs from the FDA for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of disease progression (as defined by the EUA). The FDA had previously issued an EUA for bamlanivimab alone. Due to the increase in circulating variants that have the potential

for resistance to bamlanivimab, that EUA has since been revoked.

Several circulating SARS-CoV-2 variants, particularly those that contain the mutation E484K, are associated with reduced susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro. However, the clinical impact of these mutations is not known. Reduced in vitro susceptibility to both antibodies in a combination regimen is currently uncommon. Please see [Anti-SARS-CoV-2 Monoclonal Antibodies](#) for more information regarding the circulating SARS-CoV-2 variants of concern and interest and the susceptibility of these variants to anti-SARS-CoV-2 monoclonal antibodies.

The clinical trial data that demonstrate the clinical benefit of these anti-SARS-CoV-2 monoclonal antibody combinations for the treatment of outpatients with mild to moderate COVID-19 are outlined below. It is worth noting that these studies were conducted before the widespread circulation of the variants of concern.

### ***Clinical Data***

#### **Bamlanivimab Plus Etesevimab**

The EUA for bamlanivimab plus etesevimab was based on data from several studies, including the [Blocking Viral Attachment and Cell Entry With SARS-CoV-2 Neutralizing Antibodies](#) (BLAZE)-1 and [BLAZE-4](#) trials.

In the Phase 3 BLAZE-1 trial, a randomized trial that included 1,035 high-risk participants, the primary endpoint was the proportion of participants who had a COVID-19-related hospitalization (defined as  $\geq 24$  hours of acute care) or who died from any cause by Day 29. Compared to those who received placebo, participants who received bamlanivimab 2,800 mg plus etesevimab 2,800 mg had a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death from any cause; endpoint events occurred in 11 of 518 participants (2.1%) in the bamlanivimab plus etesevimab arm and in 36 of 517 participants (7.0%) in the placebo arm ( $P = 0.0004$ ). There were no deaths in the bamlanivimab plus etesevimab arm, and 10 deaths occurred in the placebo arm.<sup>13,14</sup>

Of note, the doses authorized in the EUA (bamlanivimab 700 mg plus etesevimab 1,400 mg) are different from the doses studied in the Phase 3 BLAZE-1 study. The available data suggest that the antiviral activity of this lower dose is similar to that of bamlanivimab 2,800 mg plus etesevimab 2,800 mg.<sup>14</sup>

#### **Casirivimab Plus Imdevimab**

The recommendation for the use of casirivimab plus imdevimab is based on Phase 3 results from the [R10933-10987-COV-2067](#) study (the information from this study is currently available only in a press release, and there is no peer-reviewed preprint or publication).<sup>15</sup> This trial compared 1,355 participants who received casirivimab 1,200 mg plus imdevimab 1,200 mg to 1,341 participants who received placebo.

The modified full analysis set included participants who were aged  $\geq 18$  years and had a positive SARS-CoV-2 polymerase chain reaction result from a nasopharyngeal swab at randomization and one or more risk factors for severe COVID-19. COVID-19-related hospitalizations or death from any cause were reported in 18 of 1,355 participants (1.3%) in the casirivimab plus imdevimab arm and in 62 of 1,341 participants (4.6%) in the placebo arm ( $P < 0.0001$ ). This represents a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death in the casirivimab plus imdevimab treatment participants.

### **Patients Who Are Hospitalized With Moderate COVID-19 but Who Do Not Require Supplemental Oxygen**

#### ***Recommendations***

- The Panel **recommends against** the use of **dexamethasone** or **other corticosteroids (AIIa)**. Patients who are receiving dexamethasone or another corticosteroid for other indications should

continue therapy for their underlying conditions as directed by their health care provider.

- There are insufficient data to recommend either for or against the routine use of remdesivir in these patients. The use of remdesivir may be appropriate in patients who have a high risk of disease progression.

### ***Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids***

In the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive either dexamethasone plus standard of care or standard of care alone (control arm).<sup>7</sup> In the subgroup of participants who did not require supplemental oxygen at enrollment, no survival benefit was observed for dexamethasone: 17.8% of participants in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). Please see [Table 4a](#) for additional information. Based on these data, the Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19 in this subgroup, unless the patient has another indication for corticosteroid therapy.

### ***Rationale for the Panel’s Assessment That There Are Insufficient Data to Recommend Either for or Against the Use of Remdesivir***

The Adaptive COVID-19 Treatment Trial (ACTT-1) was a multinational randomized controlled trial that compared remdesivir to placebo in hospitalized patients with COVID-19. Remdesivir showed no significant benefit in patients with mild to moderate disease, which was defined as oxygen saturation >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen (rate ratio for recovery 1.29; 95% CI, 0.91–1.83); however, there were only 138 patients in this group.<sup>3</sup>

In a manufacturer-sponsored, open-label randomized trial of 596 patients with moderate COVID-19, patients who received 5 days of remdesivir had higher odds of having a better clinical status on Day 11 (based on distribution on a seven-point ordinal scale) than those who received standard of care (OR 1.65; 95% CI, 1.09–2.48;  $P = 0.02$ ). However, the difference between the groups was of uncertain clinical importance.<sup>5</sup>

The Solidarity trial was a large, multinational, open-label randomized controlled trial in which a 10-day course of remdesivir was compared to standard of care. About 25% of hospitalized patients in the remdesivir and control arms did not require supplemental oxygen at study entry. The primary outcome of in-hospital mortality occurred in 11 of 661 patients (2%) in the remdesivir arm and in 13 of 664 patients (2.1%) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).<sup>16</sup> The open-label design of this study makes it difficult to determine whether remdesivir affects recovery time as determined by duration of hospitalization, because patient discharge may have been delayed in order to complete remdesivir therapy. Please see [Table 2a](#) for additional information.

Because these trials produced conflicting results regarding the benefits of remdesivir, the Panel finds the available data insufficient to recommend either for or against routine treatment with remdesivir for all hospitalized patients with moderate COVID-19. However, the Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate disease (e.g., a person who is at a particularly high risk for clinical deterioration).

## For Hospitalized Patients With COVID-19 Who Require Supplemental Oxygen but Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or Extracorporeal Membrane Oxygenation

### *Recommendations*

The Panel recommends one of the following options for these patients:

- **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) (**BIIa**);
- **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) (**BIII**); *or*
- **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (**BI**).

### *Additional Considerations*

- If dexamethasone is not available, an alternative corticosteroid such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used (**BIII**). See [Corticosteroids](#) for dosing recommendations.
- In the rare circumstances when corticosteroids cannot be used, **baricitinib plus remdesivir** can be used (**BIIa**). Baricitinib **should not be used** without remdesivir.
- There is insufficient evidence to determine which patients in this group would benefit from adding tocilizumab to dexamethasone treatment. Some Panel members would add tocilizumab to a patient's dexamethasone treatment in cases where the patient has rapidly increasing oxygen needs and C-reactive protein (CRP) levels  $\geq 75$  mg/L but does not yet require oxygen through high-flow nasal canula (HFNC) or noninvasive ventilation.

### *Rationale for the Use of Remdesivir*

In ACTT-1, remdesivir was associated with improved time to recovery in the subgroup of participants ( $n = 435$ ) who required oxygen supplementation but not high-flow oxygen, noninvasive ventilation, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). A lower percentage of patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) among those who were not using these methods of oxygen delivery at baseline (17% vs. 24%). In a post hoc analysis of deaths by Day 29, remdesivir appeared to confer a substantial survival benefit in this subgroup (HR for death 0.30; 95% CI, 0.14–0.64).<sup>3</sup>

The Solidarity trial reported no difference in the rate of in-hospital deaths between patients who received remdesivir and those who received standard of care (rate ratio for death in the overall study population 0.95; 95% CI, 0.81–1.11; rate ratio for death in patients who did not require mechanical ventilation at entry 0.86; 99% CI, 0.67–1.11). There was no difference between patients who received remdesivir and those who received standard of care in the percentage of patients who progressed to invasive mechanical ventilation (11.9% vs. 11.5%) or in length of hospital stay.<sup>16</sup> However, an open-label trial like Solidarity is less well-suited to assess time to recovery than a placebo-controlled trial. In Solidarity, because both clinicians and patients knew that remdesivir was being administered, it is possible that the hospital discharge could have been delayed in order to complete the 10-day course of therapy.

Based on the results of ACTT-1, the Panel recommends **remdesivir** (without dexamethasone) as a treatment option for certain patients who require supplemental oxygen (e.g., those who require minimal supplemental oxygen) (**BIIa**). In these individuals, the hyperinflammatory state where corticosteroids might be most beneficial may not yet be present or fully developed. For more information, please see [Table 2a](#).

### ***Rationale for the Use of Remdesivir Plus Dexamethasone***

The safety and efficacy of using remdesivir plus dexamethasone for the treatment of COVID-19 have not been rigorously evaluated in clinical trials. Despite the lack of clinical trial data, there is a theoretical rationale for combining remdesivir and dexamethasone (see the discussion of clinical trial data for remdesivir above and the discussion for dexamethasone below). Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection.

Based on these theoretical considerations, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients in this group (e.g., those who require increasing amounts of supplemental oxygen) (**BIII**).

### ***Rationale for the Use of Dexamethasone***

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen at enrollment. In the dexamethasone group, 23.3% of participants died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).<sup>7</sup> However, the amount of supplemental oxygen that participants were receiving and the proportions of participants who required oxygen delivery through a high-flow device or noninvasive ventilation were not reported. It is possible that the benefit of dexamethasone was greatest in those who required more respiratory support. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. For more information, please see the [Corticosteroids](#) section.

However, some experts prefer not to use dexamethasone monotherapy in this group because of the theoretical concern that corticosteroids might slow viral clearance when they are administered without an antiviral drug. Corticosteroids have been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections.<sup>17-19</sup> Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.<sup>20-24</sup>

### ***Rationale for the Use of Baricitinib Plus Remdesivir When Corticosteroids Cannot Be Administered***

In ACTT-2, 1,033 hospitalized patients with COVID-19 were randomized to receive baricitinib (a Janus kinase inhibitor) plus remdesivir or placebo plus remdesivir. Among all participants, the median time to recovery was shorter with baricitinib plus remdesivir (7 days) than with remdesivir alone (8 days; rate ratio 1.16; 95% CI, 1.01–1.32;  $P = 0.03$ ). New use of oxygen or mechanical ventilation was less likely with baricitinib plus remdesivir than with remdesivir alone, as were serious adverse events and new infections.

In a subgroup analysis of participants who required supplemental oxygen but who did not receive it through a high-flow device or invasive mechanical ventilation, the rate ratio for recovery was 1.17 (95% CI, 0.98–1.39). There was no statistically significant difference in mortality by Day 28 between the baricitinib and placebo arms in this subgroup (OR 0.4; 95% CI, 0.14–1.14) or in the overall population. Baseline corticosteroid use was an exclusion criterion, and the trial enrolled most participants prior to the public release of RECOVERY data.

Because dexamethasone has been shown to reduce mortality among patients who required supplemental oxygen, clinicians should prioritize the use of dexamethasone in this subgroup. The Panel therefore reserves **baricitinib plus remdesivir** for the rare circumstances in which corticosteroids are contraindicated (**BIIa**). It is unknown whether baricitinib would have an additive benefit or adverse

effects when given in combination with corticosteroids. Therefore, the Panel **recommends against** using the combination of **baricitinib, dexamethasone, and remdesivir**, except in a clinical trial (**BIII**). It is also unknown whether baricitinib would have an additive benefit or adverse effects when given in combination with tocilizumab. Therefore, the Panel **recommends against** using the combination of **baricitinib and tocilizumab**, except in a clinical trial (**BIII**).

### ***Rationale for the Panel’s Assessment That There Are Insufficient Data to Determine Which Patients Would Benefit From Dexamethasone Plus Tocilizumab***

Early trials that evaluated the use of tocilizumab in patients who were hospitalized with COVID-19 did not show a treatment effect for tocilizumab. These trials included a high proportion of patients who were receiving conventional oxygen therapy; however, many of these trials were underpowered, and only a small proportion of patients were also receiving corticosteroids.<sup>25-29</sup> Although the RECOVERY trial reported a mortality benefit for tocilizumab, the study did not identify a particular subgroup of hospitalized patients on conventional oxygen therapy who benefited most from receiving the drug.<sup>12</sup> Among 21,550 participants who were randomized into the RECOVERY platform trial, only 4,116 of the participants (19%) underwent a second randomization into the tocilizumab intervention arm, suggesting that the study results are generalizable only to a restricted subset of hospitalized patients. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the RECOVERY trial suggests that patients with clinical evidence of progressive COVID-19 were preferentially selected for the tocilizumab study.

The Panel recognizes that there may be some hospitalized patients who are receiving conventional oxygen therapy who may have progressive hypoxemia associated with significant systemic inflammation. The addition of tocilizumab to their standard treatment may provide a modest benefit. Nevertheless, there is insufficient evidence to clearly characterize the subgroups within this patient population who would benefit from receiving tocilizumab.

## **For Hospitalized Patients With COVID-19 Who Require Delivery of Oxygen Through a High-Flow Device or Noninvasive Ventilation but Not Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation**

### ***Recommendations***

- The Panel recommends one of the following options for these patients:
  - **Dexamethasone** alone (**AI**); *or*
  - A combination of **dexamethasone plus remdesivir** (**BIII**).
- For patients who were recently hospitalized and who have rapidly increasing oxygen needs and systemic inflammation, add **tocilizumab** to one of the two options above (**BIIa**).

### ***Additional Considerations***

- The combination of dexamethasone and remdesivir has not been rigorously studied in clinical trials. Because there are theoretical reasons for combining these drugs, the Panel considers both dexamethasone alone and the combination of remdesivir and dexamethasone to be acceptable options for treating COVID-19 in this group of patients.
- The Panel **recommends against** the use of **remdesivir alone** because it is not clear whether remdesivir confers a clinical benefit in this group of patients (**AIIa**).
- For patients who initially received remdesivir monotherapy and progressed to requiring high-flow oxygen or noninvasive ventilation, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.

- If dexamethasone is not available, equivalent doses of other corticosteroids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** may be used (**BIII**). See [Corticosteroids](#) for more information.
- In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used (**BIIa**). Baricitinib **should not be used** without remdesivir.
- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Some clinicians may choose to assess a patient’s clinical response to dexamethasone before deciding whether tocilizumab is needed.
- Although some patients in the Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physicians, there are insufficient data to determine which patients, if any, would benefit from an additional dose of the drug.
- The combination of dexamethasone and tocilizumab may increase the risk of opportunistic infections or reactivation. Prophylactic treatment with ivermectin should be considered for patients who are from areas where strongyloidiasis is endemic.

### ***Rationale for the Use of Dexamethasone***

In the RECOVERY study, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen without invasive mechanical ventilation at enrollment: 23.3% of the participants in the dexamethasone group died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).<sup>7</sup>

### ***Rationale for the Use of Remdesivir Plus Dexamethasone***

The combination of remdesivir and dexamethasone has not been rigorously studied in clinical trials; therefore, the safety and efficacy of this combination are unknown. The Panel recognizes that there are theoretical reasons to use the combination of remdesivir and dexamethasone, as described above. Based on these theoretical considerations, the Panel considers the combination of dexamethasone plus remdesivir a treatment option for patients in this group (e.g., in those who require delivery of oxygen through a high-flow device or noninvasive ventilation).

### ***Rationale for Not Recommending Remdesivir Monotherapy***

In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit for remdesivir at Day 29.<sup>3</sup> However, the trial was not powered to detect differences in outcomes within subgroups. The Panel **does not recommend** using **remdesivir monotherapy** in these patients because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup (**AIIa**). Dexamethasone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

For patients who start remdesivir monotherapy and then progress to requiring oxygen delivery through a high-flow device or noninvasive ventilation, the Panel recommends initiating dexamethasone and continuing remdesivir until the treatment course is completed. Clinical trials that evaluated the use of remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; therefore, patients may benefit from remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

## ***Rationale for Recommending the Combination Use of Tocilizumab and Dexamethasone in Certain Hospitalized Patients***

The REMAP-CAP and RECOVERY studies, the two largest randomized controlled tocilizumab trials to date, have both reported a mortality benefit for tocilizumab among patients with rapid respiratory decompensation who require oxygen delivery through HFNC or noninvasive ventilation.<sup>11,12</sup> Corticosteroids were given to a majority of patients in both studies. In REMAP-CAP, a narrowly defined population of patients who were admitted to an intensive care unit (ICU) with severe to critical COVID-19 and who were exhibiting rapid respiratory decompensation were randomized to receive open-label tocilizumab or usual care alone. Compared to usual care, the use of tocilizumab reduced in-hospital mortality (28% vs. 36%) and increased the number of days free of respiratory and cardiovascular organ support (10 days vs. 0 days; OR 1.64; 95% CI, 1.25–2.14). Enrollment occurred within 24 hours of ICU admission and within a median of 1.2 days of hospitalization (IQR 0.8–2.8 days), suggesting that the benefit of tocilizumab occurs specifically in patients who are experiencing rapid respiratory decompensation. In REMAP-CAP, the evidence for therapeutic benefit was strongest among recipients who had recently started oxygen supplementation through HFNC or noninvasive ventilation, though the lack of subgroup analyses by oxygen requirement is a notable limitation of this study.

The RECOVERY trial also suggested a mortality benefit for tocilizumab plus dexamethasone in patients who specifically required noninvasive ventilation or HFNC. In this study, a subset of participants with hypoxemia and CRP levels  $\geq 75$  mg/L were offered enrollment into a second randomization to receive tocilizumab or usual care. Tocilizumab reduced all-cause mortality in these patients; 29% of participants in the tocilizumab arm had died by Day 28 compared to 33% of participants in the usual care arm (rate ratio 0.86; 95% CI, 0.77–0.96).

The Panel **recommends against** using **tocilizumab** without concomitant corticosteroids, as multiple trials have reported that the clinical benefit of tocilizumab is seen among patients who are receiving tocilizumab plus a corticosteroid (see [Table 4b](#)).

## ***Rationale for Using Baricitinib Plus Remdesivir When Corticosteroids Are Contraindicated***

During ACTT-2, the median time to recovery was shorter in the baricitinib plus remdesivir arm (7 days) than in the placebo plus remdesivir arm (8 days) in the overall study population (rate ratio 1.16; 95% CI, 1.01–1.32;  $P = 0.03$ ). In a subgroup analysis of participants who required high-flow oxygen or noninvasive ventilation ( $n = 216$ ), the median time to recovery was 10 days in the baricitinib plus remdesivir arm and 18 days in the remdesivir alone arm (rate ratio 1.51; 95% CI, 1.10–2.08). There was no statistically significant difference in mortality by Day 28 between the baricitinib and placebo arms (OR 0.65; 95% CI, 0.39–1.09) in the overall population.

Baseline corticosteroid use was an exclusion criterion, and the trial enrolled most participants prior to the public release of RECOVERY data. It is unknown whether baricitinib would have an additive benefit to treatment with corticosteroids, or whether baricitinib is safer or more efficacious than corticosteroids. Because dexamethasone has been shown to reduce mortality in patients with COVID-19 who required supplemental oxygen, clinicians should prioritize the use of dexamethasone over the use of baricitinib in this group of patients. The Panel therefore reserves **baricitinib in combination with remdesivir** for the rare circumstance in which corticosteroids are contraindicated for this subgroup (**BIIa**). It is unknown whether baricitinib would have an additive benefit or adverse effects when given in combination with corticosteroids. Therefore, the Panel **recommends against** using the combination of **baricitinib, dexamethasone, and remdesivir**, except in a clinical trial (**BIII**). It is also unknown whether baricitinib would have an additive benefit or adverse effects when given in combination with tocilizumab. Therefore, the Panel **recommends against** using the combination of **baricitinib and tocilizumab**, except in a clinical trial (**BIII**).

## For Hospitalized Patients With COVID-19 Who Require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

### *Recommendations*

- The Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO (**AI**).

### *Additional Considerations*

- If dexamethasone is not available, equivalent doses of alternative corticosteroids such as **prednisone, methylprednisolone, or hydrocortisone** may be used (**BIII**).
- For patients who initially received remdesivir monotherapy and progressed to requiring invasive mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- The Panel **recommends against** the use of **remdesivir monotherapy (AIIa)**.
- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physicians, there are insufficient data to determine which patients, if any, would benefit from an additional dose of the drug.
- The combination of dexamethasone and tocilizumab may increase the risk of opportunistic infections or reactivation. Prophylactic treatment with ivermectin should be considered for patients who are from areas where strongyloidiasis is endemic.

### *Rationale for the Use of Dexamethasone Monotherapy*

As the disease progresses in patients with COVID-19, a systemic inflammatory response may lead to multiple organ dysfunction syndrome. The anti-inflammatory effects of corticosteroids mitigate the inflammatory response, and the use of corticosteroids has been associated with improved outcomes in people with COVID-19 and critical illness.

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated seven randomized trials and included data on 1,703 critically ill patients.<sup>30</sup> The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included.<sup>7</sup> For details about the meta-analysis and the RECOVERY trial, see the [Corticosteroids](#) section. Because the benefits outweigh the potential harms, the Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO (**AI**).

### *Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy*

Dexamethasone plus remdesivir combination therapy has not been evaluated in controlled studies; therefore, there is insufficient information to make a recommendation either for or against the use of this combination therapy. There is, however, a theoretical reason to administer dexamethasone plus remdesivir to patients who have recently been intubated. Antiviral therapy may prevent a steroid-related delay in viral clearance. This delay has been reported in the setting of other viral infections.<sup>17,18</sup>

Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the studies to date are not definitive. For example, an observational study in people with non-severe COVID-19 suggested that viral clearance was delayed in patients who received corticosteroids,<sup>31</sup> whereas a more recent study

in patients with moderate to severe COVID-19 found no relationship between the use of corticosteroids and the rate of viral clearance.<sup>24</sup> Given the conflicting results from observational studies and the absence of clinical trial data, some Panel members would coadminister **dexamethasone and remdesivir** in patients who have recently been placed on mechanical ventilation (**CIII**) until more conclusive evidence becomes available, based on their concerns about delayed viral clearance in patients who received corticosteroids. Other Panel members would not coadminister these drugs due to uncertainties about the benefit of using remdesivir in critically ill patients.

### ***Rationale for Recommending the Use of Tocilizumab Plus Dexamethasone in Patients Within 24 Hours of Admission to the Intensive Care Unit***

The REMAP-CAP and RECOVERY studies, the two largest randomized controlled tocilizumab trials to date, have both reported a mortality benefit for tocilizumab among patients who were recently admitted to the ICU with rapid respiratory decompensation, including those who required invasive mechanical ventilation.<sup>11,12</sup> REMAP-CAP enrolled patients within 24 hours of admission to the ICU. Prior trials that enrolled patients later in the ICU course and/or who received oxygen support >24 hours after ICU admission have failed to show consistent clinical benefits from tocilizumab (see [Table 4b](#)). Thus, it is unclear whether there is a clinical benefit for tocilizumab in patients who received invasive mechanical ventilation more than 24 hours after ICU admission. Findings from RECOVERY suggest a clinical benefit for tocilizumab among patients with rapid clinical progression who received invasive mechanical ventilation, tocilizumab, and corticosteroids. See the section above for additional details on the clinical trial data and rationale for using tocilizumab in this situation.

### ***Rationale for Recommending Against the Use of Remdesivir Monotherapy***

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require invasive mechanical ventilation or ECMO. During ACTT-1, remdesivir did not improve the recovery rate in this subgroup of participants (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and in a post hoc analysis of deaths by Day 29, remdesivir did not improve survival among participants in this subgroup (HR 1.13; 95% CI, 0.67–1.89).<sup>3</sup> In the Solidarity trial, there was a trend toward increased mortality among patients who received mechanical ventilation and who were randomized to receive remdesivir rather than standard of care (rate ratio 1.27; 95% CI, 0.99–1.62).<sup>16</sup> Taken together, these results do not demonstrate a clear benefit of remdesivir in critically ill patients.

For patients who start remdesivir monotherapy and then progress to requiring invasive mechanical ventilation or ECMO, the Panel recommends initiating dexamethasone and continuing remdesivir until the treatment course is completed. Clinical trials that evaluated remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; therefore, patients may benefit from receiving remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

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