Symptom management should be initiated for all nonhospitalized adults with mild to moderate COVID-19. For adults who are at high risk of progression to severe disease, several antiviral therapeutic options are available to reduce the risk of hospitalization or death. The COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations on the use of these drugs for the treatment of COVID-19 are outlined in this section.

Several factors affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications, the potential for significant drug-drug interactions, the patient’s pregnancy status, and the in vitro activities of the available products against the currently circulating SARS-CoV-2 variants and subvariants.

Older adults and people who have underlying medical conditions are at increased risk of severe COVID-19. In addition, people who are members of racial and ethnic minority groups have higher rates of hospitalization and death from COVID-19 than people who are White. Disparities in the provision of anti-SARS-CoV-2 monoclonal antibody (mAb) and antiviral treatments to patients who are not White have been reported; therefore, attention to equitable access is critical.

Clinical trials supporting the use of the currently available treatment options were largely conducted in individuals who were not vaccinated; thus, the efficacy of these treatments in patients who have been vaccinated is unclear. When deciding whether to prescribe antiviral treatment (including an anti-SARS-CoV-2 mAb) to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (i.e., >4–6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of the risk factors affects the level of risk.

Table 2a outlines the Panel’s recommendations for using these therapeutic interventions outside the hospital inpatient setting.

Table 2a. Therapeutic Management of Nonhospitalized Adults With COVID-19

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>Panel’s Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does Not Require Hospitalization or Supplemental Oxygen</td>
<td>For All Patients:</td>
</tr>
<tr>
<td></td>
<td>• All patients should be offered symptomatic management (AIII).</td>
</tr>
<tr>
<td></td>
<td>• The Panel recommends against the use of dexamethasone or other systemic corticosteroids in the absence of another indication (AIIb).</td>
</tr>
<tr>
<td></td>
<td>For Patients Who Are at High Risk of Progressing to Severe COVID-19</td>
</tr>
<tr>
<td></td>
<td>Preferred therapies. Listed in order of preference:</td>
</tr>
<tr>
<td></td>
<td>• Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)</td>
</tr>
<tr>
<td></td>
<td>• Remdesivir (BIIa)</td>
</tr>
<tr>
<td></td>
<td>Alternative therapies. For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:</td>
</tr>
<tr>
<td></td>
<td>• Bebtelovimab (CIII)</td>
</tr>
<tr>
<td></td>
<td>• Molnupiravir (CIIa)</td>
</tr>
<tr>
<td>Discharged From Hospital Inpatient Setting in Stable Condition, Even if Receiving Supplemental Oxygen</td>
<td>The Panel recommends against continuing the use of remdesivir (Alla), dexamethasone or baricitinib (Alla) after hospital discharge.</td>
</tr>
</tbody>
</table>
There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.

For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. When deciding whether to prescribe antiviral treatment (including an anti-SARS-CoV-2 mAb) to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (i.e., >4–6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of the risk factors affects the level of risk.

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.

Administration of remdesivir requires 3 consecutive days of IV infusion.

Bebtelovimab is active in vitro against all circulating Omicron subvariants, but there are no clinical efficacy data from placebo-controlled trials that evaluated the use of bebtelovimab in patients who are at high risk of progressing to severe COVID-19. Therefore, bebtelovimab should be used only when the preferred treatment options are not available, feasible to use, or clinically appropriate.

Molnupiravir appears to have lower efficacy than the preferred treatment options. Therefore, it should be used only when the preferred options are not available, feasible to use, or clinically appropriate.

The Panel recommends against the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (AIII).

**Patient Prioritization for Treatment**

When there are no logistical or supply constraints, the Panel recommends prescribing therapies for the treatment of COVID-19 for any eligible individual as recommended in these Guidelines. During surges in cases of SARS-CoV-2 infection, logistical or supply constraints may make it impossible to offer available therapeutics to all nonhospitalized patients who are eligible to receive them. In these situations, the Panel recommends prioritizing the treatment of patients who are at the highest risk of clinical progression (see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints).

Table 2b. Dosing Regimens for the Drugs Listed in Table 2a

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Time From Symptom Onseta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir-Boosted Nirmatrelvir (Paxlovid)</td>
<td>- eGFR ≥60 mL/min: Nirmatrelvir 300 mg with RTV 100 mg PO twice daily for 5 days</td>
<td>≤5 days</td>
</tr>
<tr>
<td></td>
<td>- eGFR ≥30 to &lt;60 mL/min: Nirmatrelvir 150 mg with RTV 100 mg PO twice daily for 5 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- eGFR &lt;30 mL/min: Not recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Severe Hepatic Impairment (Child-Pugh Class C): Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

**Key:** CDC = Centers for Disease Control and Prevention; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel

---

*a There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.

*b For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. When deciding whether to prescribe antiviral treatment (including an anti-SARS-CoV-2 mAb) to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (i.e., >4–6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of the risk factors affects the level of risk.

*c Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

*d If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.

*e Administration of remdesivir requires 3 consecutive days of IV infusion.

*f Bebtelovimab is active in vitro against all circulating Omicron subvariants, but there are no clinical efficacy data from placebo-controlled trials that evaluated the use of bebtelovimab in patients who are at high risk of progressing to severe COVID-19. Therefore, bebtelovimab should be used only when the preferred treatment options are not available, feasible to use, or clinically appropriate.

*g Molnupiravir appears to have lower efficacy than the preferred treatment options. Therefore, it should be used only when the preferred options are not available, feasible to use, or clinically appropriate.

*h The Panel recommends against the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (AIII).
Symptom Management

Treatment of symptoms includes using over-the-counter antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough. Patients should be advised to drink fluids regularly to avoid dehydration. Rest is recommended as needed during the acute phase of COVID-19, and ambulation and other forms of activity should be increased according to the patient’s tolerance. Patients should be educated about the variability in time to symptom resolution and complete recovery. When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care (AIII).

At a minimum, health care providers should use telehealth to closely follow patients with dyspnea, and in-person monitoring of these patients should be considered (AIII). Patients with persistent or progressive dyspnea, especially those who have an oxygen saturation measured by pulse oximetry ≤94% on room air at sea level or have symptoms that suggest high acuity (e.g., chest pain or tightness, dizziness, confusion, other mental status changes), should be referred to a health care provider for an in-person evaluation (AIII).

Rationale for the Use of Specific Agents Listed in Table 2a

The Panel’s recommendations for the antiviral agents that are used to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression are based on the results of clinical trials (for ritonavir-boosted nirmatrelvir, remdesivir, and molnupiravir) and on laboratory assessments of the activity of the anti-SARS-CoV-2 mAb bebtelovimab.

The Panel recommends ritonavir-boosted nirmatrelvir and remdesivir as preferred therapeutic options because Phase 3, randomized, placebo-controlled trials have reported high clinical efficacies for these agents in high-risk patients with COVID-19 who are unvaccinated.5,6 The Panel favors the use of ritonavir-boosted nirmatrelvir in most high-risk, nonhospitalized patients with mild to moderate COVID-19. If ritonavir-boosted nirmatrelvir is not available or clinically appropriate because of drug-drug interactions, the Panel recommends using remdesivir as the second option.

The Panel recommends bebtelovimab and molnupiravir as alternative therapeutic options. These drugs should ONLY be used when neither of the preferred treatment options are available, feasible to use, or clinically appropriate. The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for bebtelovimab based on in vitro data that showed that bebtelovimab has activity against all circulating Omicron subvariants and clinical efficacy data from a small, Phase 2 clinical trial.

Table 2b. Dosing Regimens for the Drugs Listed in Table 2a, continued

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Time From Symptom Onseta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>RDV 200 mg IV on Day 1, followed by RDV 100 mg IV once daily on Days 2 and 3. Each infusion should be administered over 30–120 minutes. Patients should be observed for ≥1 hour after infusion as clinically appropriate.</td>
<td>≤7 days</td>
</tr>
<tr>
<td>Bebtelovimab</td>
<td>BEB 175 mg as a single IV injection, administered over ≥30 seconds. Patients should be observed for ≥1 hour after injection.</td>
<td>≤7 days</td>
</tr>
<tr>
<td>Molnupiravir</td>
<td>Molnupiravir 800 mg PO twice daily for 5 days</td>
<td>≤5 days</td>
</tr>
</tbody>
</table>

a Per EUA criteria or clinical trial entry criteria.
b See Remdesivir for a discussion of RDV use in patients with renal impairment.

Key: BEB = bebtelovimab; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; IV = intravenous; PO = orally; RDV = remdesivir; RTV = ritonavir
in individuals with mild to moderate COVID-19 who were at low risk of disease progression. However, there are no Phase 3 clinical trial data for bebtelovimab. Molnupiravir appears to have had lower clinical efficacy in Phase 3 clinical trials than the preferred treatment options, although there are no direct comparisons of these therapies.

There are currently no clinical trial data that directly compare the clinical efficacies of the 4 recommended therapies, and there are no data on the use of combinations of antiviral agents and/or anti-SARS-CoV-2 mAbs for the treatment of COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19. The rationale for each of the Panel’s recommendations is discussed below.

**Ritonavir-Boosted Nirmatrelvir (Paxlovid)**

Nirmatrelvir is an orally bioavailable protease inhibitor that is active against \( \text{M}^{\text{PRO}} \), a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins. It has demonstrated antiviral activity against all coronaviruses that are known to infect humans. The FDA issued an EUA for ritonavir-boosted nirmatrelvir for the treatment of mild to moderate COVID-19 in nonhospitalized adults and pediatric patients aged ≥12 years and weighing ≥40 kg who are at high risk of disease progression. Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent. Ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range.

**Recommendation**

- The Panel recommends using nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid) orally (PO) twice daily for 5 days in nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression; treatment should be initiated as soon as possible and within 5 days of symptom onset (AIIa).

**Additional Considerations**

- Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir because there are concerns that a shorter treatment course may be less effective or lead to resistance.
- If a patient requires hospitalization after starting treatment, the full 5-day treatment course of ritonavir-boosted nirmatrelvir should be completed unless there are drug-drug interactions that preclude its use.
- For considerations in pregnancy, see [Ritonavir-Boosted Nirmatrelvir (Paxlovid)].
- Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination.
- Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient’s concomitant medications, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions.
- A quick reference guide is also provided in [Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications]. The FDA EUA fact sheet for ritonavir-boosted nirmatrelvir, the [Liverpool COVID-19 Drug Interactions website], and guidance from the [Ontario COVID-19 Science Advisory Table] should also be used to identify and manage drug-drug interactions.

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 88% compared to placebo in nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection. This efficacy is comparable to the efficacies reported in similar patient populations for remdesivir (87%
Ritonavir-boosted nirmatrelvir is expected to be active against all Omicron subvariants, although clinical efficacy data are lacking. Because ritonavir-boosted nirmatrelvir has the potential for significant drug-drug interactions with concomitant medications, this regimen may not be the optimal choice for all patients (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications). However, because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral available for the treatment of COVID-19, drug-drug interactions that can be safely managed should not preclude the use of this medication.

SARS-CoV-2 Viral Rebound
Observational studies and results from the EPIC-HR trial have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir. The frequency, mechanism, and clinical implications of these events are unclear. Viral rebound and the recurrence of COVID-19 symptoms can also occur in the absence of treatment with ritonavir-boosted nirmatrelvir. The EPIC-HR study demonstrated the benefit of ritonavir-boosted nirmatrelvir in patients who were unvaccinated and at high risk of progression to severe COVID-19. To date, recurrence of symptoms following the use of ritonavir-boosted nirmatrelvir has not been associated with progression to severe COVID-19 and should not be a reason to avoid the use of ritonavir-boosted nirmatrelvir. Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized based on the current EUA, and there are insufficient data on the efficacy of administering a second course.

Remdesivir
Remdesivir is a nucleotide prodrug of an adenosine analog that binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. It is approved by the FDA for the treatment of COVID-19 in adults and children aged ≥28 days and weighing ≥3 kg who are hospitalized with COVID-19 and for those with mild to moderate COVID-19 who are not hospitalized and are at high risk of progression to severe disease. In the PINETREE trial, nonhospitalized patients with mild to moderate COVID-19 who were unvaccinated and at high risk of progressing to severe disease received 3 days of intravenous (IV) remdesivir or placebo. Use of remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death. Remdesivir has demonstrated activity in vitro and in animal studies against the Omicron variant and its subvariants. See Remdesivir for more information.

Recommendations
- The Panel recommends using remdesivir 200 mg IV on Day 1, followed by remdesivir 100 mg IV once daily on Days 2 and 3 in nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression; treatment should be initiated as soon as possible and within 7 days of symptom onset (BIIa).
- Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion as clinically appropriate.
- For patients who started on IV remdesivir during hospitalization but were discharged from the hospital in stable condition, with or without supplemental oxygen, the Panel recommends against continuing remdesivir after discharge (AIIa).
- For considerations in pregnancy, see Remdesivir.
Because remdesivir requires IV infusions for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings. However, it is an option if ritonavir-boosted nirmatrelvir is not available.

In the randomized controlled trials that evaluated the efficacy of remdesivir in hospitalized patients, remdesivir use was discontinued at the time of hospital discharge. Therefore, the Panel recommends against continuing remdesivir in patients who started on remdesivir during hospitalization but were discharged in stable condition before completing the 5-day treatment course.

**Bebtelovimab**

Bebtelovimab is a recombinant neutralizing human mAb that binds to the spike protein of SARS-CoV-2. In vitro data suggest that bebtelovimab has activity against a broad range of SARS-CoV-2 variants, including the Omicron variant and its subvariants.\(^{26,27}\) The FDA issued an EUA for bebtelovimab for the treatment of mild to moderate COVID-19 in nonhospitalized adults and pediatric patients aged ≥12 years and weighing ≥40 kg who are at high risk of disease progression. However, to date, the clinical trial data for bebtelovimab are limited to a single Phase 2, randomized, placebo-controlled trial in patients with COVID-19 who were at low risk of progressing to severe disease. The trial showed no unexpected safety events, and patients who received bebtelovimab had more rapid viral decay than those who received the placebo.

**Recommendations**

- The Panel recommends using a single **bebtelovimab 175 mg IV injection** as an alternative therapy in nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 7 days of symptom onset (CIII).

- Bebtelovimab should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored for at least 1 hour after the injection.

- For considerations in pregnancy, see **Anti-SARS-CoV-2 Monoclonal Antibodies**.

Although data on the efficacy of bebtelovimab in reducing hospitalization and deaths for patients with COVID-19 who were at high risk of disease progression are limited, this agent has a mechanism of action that is similar to other anti-SARS-CoV-2 mAbs that have been shown to reduce rates of hospitalization or death among high-risk patients in Phase 3 trials. Therefore, the in vitro data and Phase 2 clinical trial data for bebtelovimab, along with the clinical efficacy data for other anti-SARS-CoV-2 mAbs, support the use of bebtelovimab in high-risk patients with COVID-19 when preferred treatment options are not available, feasible to use, or clinically appropriate.

**Molnupiravir**

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has exhibited antiviral activity against SARS-CoV-2 in vitro and in clinical trials.\(^{28-30}\) NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.\(^{29,31}\) The FDA issued an EUA for molnupiravir for the treatment of mild to moderate COVID-19 in nonhospitalized patients aged ≥18 years who are at high risk of disease progression and for whom alternative treatment options are not available, feasible to use, or clinically appropriate. Molnupiravir has activity against Omicron subvariants based on in vitro and animal studies.\(^{14,25,30,32}\)

As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations.
Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results; in the other study, there was no evidence for mutagenicity. The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity. In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates. The FDA has required that the manufacturer monitor genomic databases for the emergence of SARS-CoV-2 variants.

Recommendations

- The Panel recommends using **molnupiravir 800 mg PO** twice daily for 5 days as an alternative therapy in nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 5 days of symptom onset (CIIa).

- The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (AIII).

- People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. For more details, see Molnupiravir.

The MOVe-OUT trial enrolled nonhospitalized adults who were unvaccinated and at high risk of progression to severe disease in the pre-Omicron era and reported that molnupiravir reduced the rate of hospitalization or death by 31% compared to placebo. In a secondary analysis of MOVe-OUT trial data, patients who received molnupiravir and progressed to hospitalization were less likely to need respiratory interventions when compared with patients who received placebo and progressed to hospitalization. Although the different COVID-19 treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir and remdesivir are not available, feasible to use, or clinically appropriate, because molnupiravir appears to have lower efficacy than these other options. It is not yet known how often viral rebound occurs after treatment with molnupiravir.

The Panel **recommends against** the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated (AIII). Fetal toxicity has been reported in animal studies of molnupiravir. However, when other therapies are not available, pregnant patients with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks’ gestation). See Special Considerations in Pregnancy for more information.

**Immunomodulators**

**For Nonhospitalized Patients With Mild to Moderate COVID-19**

The Panel **recommends against** the use of dexamethasone or other systemic glucocorticoids to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen (AIIb). However, patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care providers (AIII).

Medicare and FDA data show a significant increase in the number of prescriptions for systemic corticosteroids among nonhospitalized patients with COVID-19 despite a lack of safety and efficacy data on the use of systemic corticosteroids in this setting. Systemic glucocorticoids may cause...
harm in nonhospitalized patients with COVID-19. Results from 1 randomized controlled trial and 1 observational cohort study did not demonstrate a clinical benefit of dexamethasone among hospitalized patients who did not require supplemental oxygen,\(^{36}\) and dexamethasone may potentially cause harm in these patients.\(^{37}\) In the RECOVERY trial, the use of dexamethasone had no effect on mortality among hospitalized patients with COVID-19 who did not require supplemental oxygen (rate ratio 1.19; 95% CI, 0.91–1.55).\(^{36}\) A large observational study of patients at Veterans Affairs hospitals reported no survival benefit for dexamethasone among patients with COVID-19 who did not require supplemental oxygen. Instead, these patients had an increased risk of 90-day mortality (HR 1.76; 95% CI, 1.47–2.12).\(^{37}\) However, hospitalized patients with COVID-19 are likely to have an increased risk of mortality compared to nonhospitalized patients, which is a limitation of observational trial data.

**For Patients Who Are Discharged From the Hospital, Even if Receiving Supplemental Oxygen**

During the RECOVERY trial, dexamethasone was stopped at the time of hospital discharge. For hospitalized patients with COVID-19, the Panel recommends against the continuation of dexamethasone after discharge (AIIa). The use of corticosteroids can lead to adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting.

In the randomized controlled trials that evaluated the efficacy of baricitinib in hospitalized patients (i.e., RECOVERY, COV-BARRIER, ACTT-2, ACTT-4), baricitinib was discontinued at the time of hospital discharge. For hospitalized patients with COVID-19, the Panel recommends against the continuation of baricitinib after discharge (AIIa).

**Other Agents That Have Been Studied or Are Under Investigation**

- The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin (AIIa), lopinavir/ritonavir, and other HIV protease inhibitors (AIII) for the outpatient treatment of COVID-19.
- The Panel recommends against the use of antibacterial therapy (e.g., azithromycin, doxycycline) for the outpatient treatment of COVID-19 in the absence of another indication (AIII).
- Other agents have undergone or are currently undergoing investigation in the outpatient setting. For more information, please refer to the sections of the Guidelines that address:
  - COVID-19 convalescent plasma
  - Miscellaneous drugs, such as colchicine, fluvoxamine, ivermectin, and inhaled corticosteroids
  - Supplements, such as vitamin C, vitamin D, and zinc
  - The Panel recommends against the use of anticoagulants and antiplatelet therapy for the prevention of venous thromboembolism or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (AIIa). For more information, see Antithrombotic Therapy in Patients With COVID-19.

**Concomitant Medication Management**

In general, a patient’s usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19 (see Considerations for Using Concomitant Medications in Patients With COVID-19). Angiotensin-converting enzyme inhibitors, statin therapy, nonsteroidal anti-inflammatory drugs, and oral, inhaled, and intranasal corticosteroids that are prescribed for comorbid conditions should be continued as directed (AIII). Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of SARS-CoV-2.\(^{38}\) In patients
with HIV, antiretroviral therapy should not be switched or adjusted for the purpose of preventing or treating SARS-CoV-2 infection (AIII). For more information, see Special Considerations in People With HIV.

When a patient is receiving an immunomodulating medication, the prescribing clinician or an expert in the subspecialty should be consulted about the risks and benefits associated with a temporary dose reduction or discontinuation. These risks and benefits will depend on the medication’s indication and the severity of the underlying condition (see Special Considerations in People Who Are Immunocompromised).

**Use of Concomitant Medications With Ritonavir-Boosted Nirmatrelvir (Paxlovid)**

Ritonavir-boosted nirmatrelvir has the potential for significant and complex drug-drug interactions with concomitant medications, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong CYP3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. However, ritonavir may also increase concentrations of certain concomitant medications, thereby increasing the potential for serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and/or drug transporters.

Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient’s concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs. Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, and the FDA EUA fact sheet for ritonavir-boosted nirmatrelvir for guidance regarding potential drug-drug interactions.

**References**


8. Pillaiyar T, Manickam M, Namavishayam V, Hayashi Y, Jung SH. An overview of severe acute respiratory


