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.

The main goal of therapeutic management for nonhospitalized patients is to prevent progression to severe disease, hospitalization, or death. Other goals may include accelerating symptom recovery, viral clearance, and prevention of long-term sequelae. Current data on the impact of therapy on these secondary goals are limited.

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, the time from symptom onset, and the in vitro activities of the available products against the currently circulating SARS-CoV-2 variants and subvariants.

Most of the data that support the use of the recommended treatment options come from clinical trials that enrolled individuals who were at high risk of disease progression and who had no pre-existing immunity from COVID-19 vaccination or prior SARS-CoV-2 infection. Accordingly, the proportion of hospitalizations and deaths in the placebo arms of these trials was high compared to what has been seen more recently in populations where most people are vaccinated or have had prior SARS-CoV-2 infection. Although these trials demonstrated the efficacy of using antiviral drugs in high-risk populations, it is difficult to know their precise effectiveness in the current setting because of the low rates of hospitalization and death among those who have been vaccinated.

Nevertheless, some patients continue to have an increased risk of disease progression, and it is in those people that therapies are most likely to be beneficial. Patients who are at the highest risk are older patients (i.e., those aged >50 years and especially those aged ≥65 years) and patients who are unlikely to have an adequate immune response to COVID-19 vaccines due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. Other risk factors include lack of vaccination or incomplete vaccination; a prolonged amount of time since the most recent vaccine dose (e.g., >6 months); and conditions such as obesity, diabetes, and chronic respiratory, cardiac, or kidney disease.¹

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.² Disparities in the use of antiviral treatments in patients who are not White have been reported; therefore, attention to equitable access is critical.³⁴

The Panel’s recommendations reflect the available data on the benefits of using antiviral therapies to prevent progression to severe COVID-19. The Panel will consider the potential benefits of available therapies for other outcomes, such as symptom recovery, as those data emerge.

Table 2a outlines the Panel’s recommendations for the therapeutic management of nonhospitalized adults with COVID-19. For recommended doses of the agents listed in Table 2a, see Table 4e.
Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>Panel’s Recommendations</th>
</tr>
</thead>
</table>
| All Patients        | • Symptom management should be initiated for all patients (AIII).  
                     | • The Panel recommends against the use of dexamethasone or other systemic corticosteroids in the absence of another indication (AIIb). |
| Patients Who Are at High Risk of Progressing to Severe COVID-19 | Preferred therapies. Listed in order of preference:  
                     | • Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa); see footnote on drug interactions.  
                     | • Remdesivir (BIIa)  
Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:  
• Molnupiravir (CIIa) |

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.

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 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 (e.g., >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 immunsuppressive medications. The number and severity of risk factors also affects the level of risk.

c For a discussion of potential treatment options for patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication, see below and Special Considerations in People Who Are Immunocompromised.

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

e 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.

f Administration of remdesivir requires an IV infusion once daily for 3 days.

g Molnupiravir appears to have lower efficacy than the other options recommended by the Panel. Therefore, it should be considered when the other 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).

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

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 Panel's Recommendations**

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. The Panel **recommends against** using anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19 (AIII) because the dominant Omicron subvariants in the United States are not expected to be susceptible to these products. See Anti-SARS-CoV-2 Monoclonal Antibodies for more information.

The Panel favors the use of ritonavir-boosted nirmatrelvir (Paxlovid) in most high-risk, nonhospitalized patients with mild to moderate COVID-19. When ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions), the Panel recommends using remdesivir. Ritonavir-boosted nirmatrelvir has high efficacy; has been shown to reduce hospitalization and death when administered to high-risk, unvaccinated, nonhospitalized patients within 5 days of symptom onset; and is an oral medication, whereas remdesivir requires intravenous (IV) administration.

The Panel’s recommendation for remdesivir is based on a Phase 3, randomized, placebo-controlled trial that reported high clinical efficacy in high-risk, nonhospitalized patients with COVID-19 who were unvaccinated. However, in some settings, daily IV administration of remdesivir for 3 days may be a logistical challenge.

The Panel recommends molnupiravir as a therapeutic option when the other recommended antiviral treatment options are not available, feasible to use, or clinically appropriate (CIIa). Molnupiravir appears to have lower clinical efficacy than the other treatment options, although no randomized studies have compared these therapies directly. The rationale for each of the Panel’s recommendations is discussed below.

Currently, data on the use of combinations of antiviral agents for the treatment of COVID-19 are limited. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.

**Strategies for the Use of Ritonavir-Boosted Nirmatrelvir**

Because ritonavir is a strong cytochrome P450 3A4 inhibitor and a P-glycoprotein inhibitor, it may increase blood concentrations of certain concomitant medications and increase the potential for serious drug toxicities. Therefore, the Food and Drug Administration (FDA) prescribing information includes a boxed warning for significant drug-drug interactions with ritonavir-boosted nirmatrelvir. Clinicians should consider both the potential benefits of treatment with ritonavir-boosted nirmatrelvir and the potential risks related to drug-drug interactions.

Many drug-drug interactions between ritonavir-boosted nirmatrelvir and concomitant medications can be safely managed (e.g., with certain statins, calcium channel blockers, or direct oral anticoagulants). If a significant drug-drug interaction is identified, prescribers should consider consulting with a pharmacist.

The following resources are available to assist in identifying and managing drug-drug interactions:

- Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant
Medications

• The Liverpool COVID-19 Drug Interactions website
• The University of Waterloo/University of Toronto drug interaction guide
• The FDA prescribing information for ritonavir-boosted nirmatrelvir

The use of ritonavir-boosted nirmatrelvir may be challenging in patients with severe renal impairment and in patients receiving certain transplant-related immunosuppressants or chemotherapy. The FDA prescribing information states that until more data are available, ritonavir-boosted nirmatrelvir is not recommended in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min. Although data on dose adjustments are limited, some groups have proposed dosing adjustments in patients with an eGFR of <30 mL/min or for patients receiving hemodialysis.

The decision to prescribe ritonavir-boosted nirmatrelvir to patients receiving calcineurin and mammalian target of rapamycin inhibitors should always be made in consultation with the patient’s specialist providers. Among reports submitted to the FDA Adverse Events Reporting System, the most commonly reported concomitant medications resulting in serious adverse reactions, including fatal events, were calcineurin inhibitors (e.g., tacrolimus). Ritonavir-boosted nirmatrelvir may be prescribed to select patients if an expert in managing the interaction is available and close therapeutic drug monitoring is logistically feasible. Otherwise, an alternative therapy for COVID-19 should be considered. See the American Society of Transplantation statement for additional information.

Interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents should also be managed in consultation with the patient’s specialist providers. For guidance on managing these interactions, refer to the FDA prescribing information for ritonavir-boosted nirmatrelvir and the prescribing information for the chemotherapeutic agent. The University Health Network/Kingston Health Sciences Centre provides an additional resource for evaluating drug-drug interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents.

Strategies for the Use of Remdesivir

Advanced planning (e.g., reserving infusion slots, identifying alternative infusion sites) may be needed to increase access to IV remdesivir. IV remdesivir can be administered in skilled nursing facilities, home health care settings, and outpatient facilities such as infusion centers. If treatment facilities cannot provide a 3-day course of remdesivir IV infusions to all eligible patients, prioritizing patients who will benefit the most from the therapy becomes necessary. The prioritization scheme below is based on 4 key elements: age, vaccination status, immune status, and clinical risk factors. For a list of risk factors, see the Centers for Disease Control and Prevention (CDC) webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. The groups are listed by tier in descending order of priority.

<table>
<thead>
<tr>
<th>Tier</th>
<th>Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status; or • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).</td>
</tr>
<tr>
<td>2</td>
<td>• Unvaccinated individuals not included in Tier 1 who are at risk of severe disease (anyone aged ≥65 years or anyone aged &lt;65 years with clinical risk factors)</td>
</tr>
<tr>
<td>3</td>
<td>• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged &lt;65 years with clinical risk factors)</td>
</tr>
</tbody>
</table>

a See the CDC website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for a discussion.
of immunocompromising conditions.

Vaccinated individuals who are not up to date with their immunizations are likely at higher risk for severe disease; patients within this tier who are in this situation should be prioritized for treatment. See the CDC webpage Stay Up to Date with COVID-19 Vaccines for more information.

See Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment of COVID-19 in Nonhospitalized Patients When There Are Logistical Constraints for more information.

Patients Who Are Immunocompromised and Have Prolonged Symptoms and Evidence of Ongoing Viral Replication

For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication (e.g., those with a low cycle threshold value, as measured by a reverse transcription polymerase chain reaction result or with a positive rapid antigen test result) despite receiving a course of antiviral therapy, the optimal management is unknown. Case reports and case series have documented the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer COVID-19 convalescent plasma (CCP), or combination therapy.\textsuperscript{13-17} The data for these approaches are not definitive, but some Panel members would use 1 or more of the following treatment options:

- Longer and/or additional courses of ritonavir-boosted nirmatrelvir
- Longer and/or additional courses of remdesivir
- High-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient’s illness

For further discussion of these potential treatment options, see Special Considerations in People Who Are Immunocompromised.

Additional Information on Ritonavir-Boosted Nirmatrelvir

Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M\textsuperscript{PRO}, a viral protease that plays an essential role in viral replication.\textsuperscript{18} The FDA has approved ritonavir-boosted nirmatrelvir for the treatment of mild to moderate COVID-19 in nonhospitalized adults who are at high risk of progressing to severe COVID-19.\textsuperscript{7}

Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir, which was shown to be efficacious in the EPIC-HR trial.\textsuperscript{5} 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.

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 89\% compared to placebo in unvaccinated, nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.\textsuperscript{5} This efficacy is comparable to the efficacies reported in similar patient populations for remdesivir (87\% relative reduction)\textsuperscript{5,7} and greater than the efficacy reported for molnupiravir in this setting (31\% relative reduction).\textsuperscript{6}

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.
For more information on the use of ritonavir-boosted nirmatrelvir, see Ritonavir-Boosted Nirmatrelvir (Paxlovid). See Viral Rebound and Symptom Recurrence below for information regarding SARS-CoV-2 viral rebound in patients who have completed treatment with ritonavir-boosted nirmatrelvir.

**Additional Information on Remdesivir**

Remdesivir is a nucleotide prodrug of an adenosine analog that inhibits SARS-CoV-2 replication. 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 progressing 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 IV remdesivir or placebo. Use of remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death.19-21

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 the infusion as clinically appropriate.

For more information, see Remdesivir.

**Additional Information on Molnupiravir**

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine, a ribonucleoside that has shown antiviral activity against SARS-CoV-2 in vitro and in clinical trials.22-24 The FDA issued an Emergency Use Authorization 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 accessible or clinically appropriate.

The MOVe-OUT trial enrolled nonhospitalized adults who were unvaccinated and at high risk of progression to severe disease in the pre-Omicron era. The study found that molnupiravir reduced the rate of hospitalization or death by 31% compared to placebo.25 A secondary analysis of MOVe-OUT trial data revealed that patients who received molnupiravir and progressed to hospitalization were less likely to need respiratory interventions than patients who received placebo and progressed to hospitalization.26

The PANORAMIC trial enrolled participants during a period when the Omicron variant was circulating.27 The participants were nonhospitalized adults with COVID-19 who were at high risk of progressing to severe disease, and 94% had received at least 3 doses of a COVID-19 vaccine. The study found that the use of molnupiravir plus usual care did not reduce the primary composite outcome of hospitalization or death compared to usual care alone. The rates of this composite outcome were low (1%) in both arms. Molnupiravir plus usual care was superior to usual care alone for several secondary clinical endpoints. For example, patients who received molnupiravir plus usual care reported recovering from COVID-19 an estimated 4 days earlier than those who received usual care alone. However, because the PANORAMIC trial was an open-label study and the patients knew whether they were receiving molnupiravir or not, this may have affected their reported symptoms. As a result, these findings are less reliable than those from a placebo-controlled trial.

Although the different COVID-19 treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir as an alternative therapy when ritonavir-boosted nirmatrelvir and remdesivir are not available, feasible to use, or clinically appropriate, because molnupiravir appears to have lower clinical efficacy than these other options.

Molnupiravir is a mutagenic ribonucleoside antiviral agent, and there is a theoretical risk that the drug will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations.
The available genotoxicity data and the 5-day duration of treatment led the FDA to conclude that molnupiravir has a low risk for genotoxicity.\textsuperscript{28}

The Panel \textbf{recommends against} the use of \textbf{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.

Fetal toxicity has been reported in animal studies of molnupiravir.\textsuperscript{28} 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 \textit{Pregnancy, Lactation, and COVID-19 Therapeutics} for more information.

For more information, see \textbf{Molnupiravir}.

\textbf{Viral Rebound and Symptom Recurrence}

Observational studies and the EPIC-HR and MOVe-OUT trials 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 or molnupiravir.\textsuperscript{7,28-31} 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.\textsuperscript{7,29-32}

To date, the recurrence of COVID-19 symptoms and virus detection following the use of antiviral therapies has not been associated with progression to severe COVID-19. Therefore, concerns about the recurrence of symptoms or viral rebound \textbf{should not} be a reason to avoid using antiviral therapies.\textsuperscript{28,33-35} There are insufficient data on whether a longer course of ritonavir-boosted nirmatrelvir or molnupiravir will prevent viral rebound or symptom recurrence. There also are insufficient data on the efficacy of administering a second course of antiviral therapy to treat viral rebound or symptom recurrence.

\textbf{Immunomodulators}

The Panel \textbf{recommends against} the use of \textbf{dexamethasone} or other systemic corticosteroids to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen (AIIb). Patients with COVID-19 who are receiving \textbf{dexamethasone} or another corticosteroid for an underlying condition should continue this therapy as directed by their health care provider (AIII).

Medicare and FDA data show a significant increase in the number of prescriptions for systemic corticosteroids among nonhospitalized patients with COVID-19\textsuperscript{36} 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,\textsuperscript{37} and dexamethasone may potentially cause harm in these patients.\textsuperscript{38}

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).\textsuperscript{37} 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).\textsuperscript{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.
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 (ACE) inhibitors; angiotensin receptor blockers (ARBs); statin therapy; nonsteroidal anti-inflammatory drugs; and oral, inhaled, and intranasal corticosteroids that are prescribed for comorbid conditions should be continued as directed (AIIa for ACE inhibitors and ARBs; AIII for other medications). Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of SARS-CoV-2.39 In patients with HIV, antiretroviral therapy should not be switched or adjusted for the theoretical 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).

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.

References


