Several therapeutic options are now available for the treatment of nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression. A number of factors may 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 (i.e., sotrovimab or remdesivir), the potential for significant drug-drug interactions (e.g., those associated with the use of ritonavir-boosted nirmatrelvir [Paxlovid]), and the regional prevalence of variants of concern (VOC).

Figure 1 outlines the COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations for using these therapeutic interventions outside the hospital inpatient setting.
a For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19 and the Patient Prioritization for Treatment section below.

b Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient’s concomitant medications and evaluate potential drug-drug interactions.

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

d The B.1.1.529 (Omicron) VOC is currently the dominant SARS-CoV-2 variant in the United States. Sotrovimab is the only anti-SARS-CoV-2 mAb that is active against the Omicron VOC.

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

f Molnupiravir has a lower efficacy than the other treatment options. Therefore, it should be used ONLY when the other options are not available or feasible.

g There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause harm.

h These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

i Provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen for the first time or are increasing their baseline oxygen requirements), pulse oximetry, laboratory monitoring, and close follow-up through visiting nurse services, telehealth, or in-person visits.

j See Therapeutic Management of Hospitalized Adults With COVID-19.

Key: AE = adverse events; CDC = Centers for Disease Control and Prevention; ED = emergency department; IV = intravenous; mAb = monoclonal antibody; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; VOC = variant of concern

Patient Prioritization for Treatment

During surges in cases of SARS-CoV-2 infection, logistical or supply constraints may make it impossible to offer available therapeutics to all the 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.

In Table A, the Panel has prioritized the risk groups for anti-SARS-CoV-2 therapy based on 4 key elements: age, vaccination status, immune status, and the presence of risk factors for clinical progression. The groups are listed in descending order of priority. For a list of risk factors, see the Centers for Disease Control and Prevention (CDC) website Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19.

Table A. Patient Risk Groups for Prioritizing the Use of Anti-SARS-CoV-2 Therapy

<table>
<thead>
<tr>
<th>Tier</th>
<th>Risk Groups</th>
</tr>
</thead>
</table>
| 1    | - Immunocompromised individuals who are not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of their vaccine status (see Immunocompromising Conditions below); or  
- Unvaccinated individuals who are at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors) |
| 2    | - Unvaccinated individuals who are at risk of severe disease and who are not included in Tier 1 (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors) |
| 3    | - Vaccinated individuals who are at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors)  
- Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely to be at higher risk for severe disease; patients who have not received a booster dose and who are within this tier should be prioritized for treatment. |
Immunocompromising Conditions

The CDC website COVID-19 Vaccines for Moderately or Severely Immunocompromised People provides a list of moderate and severe immunocompromising conditions.

If these anti-SARS-CoV-2 agents cannot be provided to all moderately to severely immunocompromised individuals because of logistical constraints or supply limitations, the Panel suggests prioritizing their use for those who are least likely to mount an adequate response to COVID-19 vaccination or SARS-CoV-2 infection and who are at risk for severe outcomes. This includes:

- Patients who are within 1 year of receiving B cell-depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients who are receiving Bruton tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid organ transplant (other than a lung transplant)
- Solid organ transplant recipients with recent treatment for acute rejection with T cell- or B cell-depleting agents
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm³

If supplies are extremely limited, the Panel suggests prioritizing those who are more severely immunocompromised (based on the list above) and who have additional risk factors for severe disease.

Table B. Dosing Regimens for the Drugs Recommended for High-Risk, Nonhospitalized Adults With Mild to Moderate COVID-19, Listed in Order of Preference Based on Efficacy and Convenience of Use

<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</td>
<td>eGFR ≥60 mL/min:</td>
<td>≤5 days</td>
</tr>
<tr>
<td>(Paxlovid)</td>
<td>• Nirmatrelvir 300 mg with RTV 100 mg PO twice daily for 5 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eGFR ≥30 to &lt;60 mL/min:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nirmatrelvir 150 mg with RTV 100 mg PO twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eGFR &lt;30 mL/min:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Not recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe Hepatic Impairment (Child-Pugh Class C):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

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Symptom Management

Symptomatic treatment includes using over-the-counter antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough. Patients with dyspnea may benefit from resting in the prone position rather than the supine position.¹ Health care providers should consider educating patients about breathing exercises, as severe breathlessness may cause anxiety.² 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.

Rationale for the Use of Specific Agents Listed in Figure 1

The Panel’s recommendations and preferences for the therapeutics that are used to treat nonhospitalized patients with COVID-19 are based on the results of clinical trials for ritonavir-boosted nirmatrelvir, remdesivir, and molnupiravir, and on the results of clinical trials and laboratory assessments of the activity of the anti-SARS-CoV-2 monoclonal antibody (mAb) products that are currently available through Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of COVID-19. These therapies are recommended for patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease.

It should be noted that a number of factors affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy and the availability of the treatment option, the feasibility of administering parenteral medications (i.e., sotrovimab, remdesivir), and the potential for significant drug-drug interactions (i.e., the interactions associated with using ritonavir-boosted nirmatrelvir).

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 cannot be used because of drug interactions, the Panel recommends using the anti-SARS-CoV-2 mAb sotrovimab as the second option. If sotrovimab is not available, then the Panel recommends using remdesivir. Molnupiravir should ONLY be used when the other 3 options are either not available or cannot be used.

There are currently no clinical trial data that directly compare the clinical efficacy of these 4 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. 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 M\(^{\text{PRO}}\), a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.\(^3\) It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.\(^4\) Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 3A4 inhibitor and pharmacokinetic boosting agent. Ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic ranges.

**Recommendation**

- The Panel recommends using nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid) orally (PO) twice daily for 5 days in those aged ≥12 years and weighing ≥40 kg; treatment should be initiated as soon as possible and within 5 days of symptom onset (AIia).
- 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.
- The EUA fact sheet for ritonavir-boosted nirmatrelvir and the Liverpool COVID-19 Drug Interactions website should be utilized to identify and manage drug-drug interactions. A quick reference guide is also provided in the Panel’s statement on the drug-drug interactions for ritonavir-boosted nirmatrelvir.

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.\(^5\) This efficacy is comparable to the efficacies reported in similar patient populations for sotrovimab (85% relative reduction),\(^6\) and remdesivir (87% relative reduction),\(^7\) and greater than the efficacy reported for molnupiravir in this setting (30% relative reduction).\(^8\)

Ritonavir-boosted nirmatrelvir is expected to be active against the B.1.1.529 (Omicron) VOC, although clinical efficacy data are lacking.\(^9\)\(^10\) Because ritonavir-boosted nirmatrelvir has the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see the Panel’s statement on the drug-drug interactions for ritonavir-boosted nirmatrelvir). However, because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral available for the treatment of COVID-19, drug interactions that can be safely managed should not preclude the use of this medication.

The EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV, which suggests that it has an acceptable safety profile during pregnancy. Based on the mechanisms of action for both nirmatrelvir and ritonavir and the available animal data, the Panel recommends ritonavir-boosted nirmatrelvir for pregnant patients because the potential benefits likely outweigh the risks.

**Sotrovimab**

Three anti-SARS-CoV-2 mAb products (bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab) have received EUAs from the FDA for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. In the clinical trials for these agents, anti-SARS-CoV-2 mAbs reduced the risk of hospitalization or death by 70% to 85%
compared to placebo. The Omicron VOC has become the dominant variant in all regions of the United States, and it is predicted to have markedly reduced susceptibility to bamlanivimab plus etesevimab and casirivimab plus imdevimab. In vitro studies indicate that sotrovimab remains active against the Omicron VOC.

**Recommendations**

- The Panel recommends using a single intravenous (IV) infusion of sotrovimab 500 mg in those aged ≥12 years and weighing ≥40 kg; treatment should be administered as soon as possible and within 10 days of symptom onset (AIIa).
- Sotrovimab 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.

Because the Omicron VOC has become the dominant variant in the United States and real-time testing for rare, non-Omicron variants is not routinely available, the Panel **recommends against** using bamlanivimab plus etesevimab or casirivimab plus imdevimab (AIII).

The data that support the EUA for sotrovimab come from the Phase 3 COMET-ICE trial, which included outpatients aged ≥18 years with mild to moderate COVID-19 who were at high risk for progressing to severe COVID-19 and were within 5 days of symptom onset. The primary endpoint of the study was the proportion of participants who were hospitalized for ≥24 hours or who died from any cause by Day 29. Endpoint events occurred in 3 of 291 participants (1%) in the sotrovimab arm and in 21 of 292 participants (7%) in the placebo arm ($P = 0.002$), resulting in a 6% absolute reduction and an 85% relative reduction (95% CI, 44% to 96%) in the risk of hospitalization or death among those who received sotrovimab. Although the study only enrolled participants who were within 5 days of symptom onset, the EUA allows sotrovimab to be used in people who are within 10 days of symptom onset.

**Remdesivir**

Remdesivir is currently approved by the FDA for use in hospitalized patients with COVID-19 and in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression. Remdesivir has been studied in nonhospitalized patients with mild to moderate COVID-19 who were at high risk of progressing to severe disease. The PINETREE trial showed that 3 consecutive days of IV remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death compared to placebo. Remdesivir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited. See the Remdesivir section for more details.

**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 those aged ≥12 years and weighing ≥40 kg; 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.

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 and sotrovimab are not available.

The Panel recommends using remdesivir, dexamethasone, or both drugs together for hospitalized patients who require supplemental oxygen (see Therapeutic Management of Hospitalized Adults With COVID-19 Treatment Guidelines).
COVID-19). When remdesivir is used in this setting, it is administered as a once-daily IV infusion for 5 days. There are rare instances when hospital resources are limited and admission to an inpatient unit is not possible for patients who need to be initiated on supplemental oxygen in the emergency department (ED) or who have increasing supplemental oxygen requirements. In this case, patients may be discharged from the ED with close monitoring and are often prescribed dexamethasone for up to 10 days. Since remdesivir is often recommended for hospitalized patients with COVID-19 who have similar oxygen needs, clinicians can consider using it in this setting. It should be noted, however, that the data on using remdesivir in this situation are limited, and administering IV infusions for up to 5 consecutive days can be difficult in the outpatient setting.

**Molnupiravir**

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.15,16

Molnupiravir has potent antiviral activity against SARS-CoV-2.15 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.17 In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA is requiring the manufacturer to establish a process to monitor genomic databases for the emergence of SARS-CoV-2 variants.

Molnupiravir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.9

**Recommendation**

- The Panel recommends using molnupiravir 800 mg PO twice daily for 5 days in those aged ≥18 years, but **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, and remdesivir are not available or cannot be used (CIII).

In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo in nonhospitalized patients with COVID-19.17 Even though the different treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir, sotrovimab, and remdesivir are not available or cannot be used, because molnupiravir has lower efficacy than the other options (CIII).

The FDA EUA states that molnupiravir is not recommended for use in pregnant patients due to concerns about the instances of fetal toxicity observed during animal studies. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks’ gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy.

People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. See the Panel’s statement on therapies for high-risk, nonhospitalized patients for more information.
Dexamethasone

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 (AIII). There is currently a lack of safety and efficacy data on the use of these agents, and systemic glucocorticoids may cause harm in these patients. 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).

In the RECOVERY trial, dexamethasone was shown to reduce mortality in hospitalized patients with COVID-19 who required supplemental oxygen.18 Nonhospitalized patients who did not require supplemental oxygen were not included in this trial. The Panel recommends against the use of dexamethasone or other systemic glucocorticoids in this population, as there are no clinical trial data to support their use (AIII).

Dexamethasone was stopped at the time of hospital discharge during the RECOVERY trial. For hospitalized patients with COVID-19 who do not require supplemental oxygen after discharge, the Panel recommends against the continuation of dexamethasone (AIIa).

In some cases, adult patients are deemed to be stable enough to be discharged from the inpatient setting even though they still require supplemental oxygen. This practice was likely uncommon during the RECOVERY trial; therefore, there is insufficient evidence to recommend either for or against the continued use of dexamethasone after hospital discharge in patients who require supplemental oxygen. 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. If a patient continues to receive corticosteroids after discharge, consider continuing corticosteroids for the duration of supplemental oxygen. However, the total duration of corticosteroid use should not exceed 10 days (including days during hospitalization). Only patients who showed good tolerance to this therapy prior to discharge should continue to receive corticosteroids after discharge, and these patients should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

In rare cases, patients with COVID-19 who require supplemental oxygen and hospital admission may need to be discharged from the ED due to scarce resources (e.g., in cases where hospital beds or staff are not available). For these patients, the Panel recommends using dexamethasone 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events (BIII). These patients should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

Other Agents That Have Been Studied or Are Under Investigation for Use in Outpatients With COVID-19

- The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin (AI), 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:
  - Antiviral agents, such as ivermectin and nitazoxanide
• **Convalescent plasma**
• **Immunomodulators**, such as colchicine, fluvoxamine, 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**.
- Health care providers should provide information about ongoing clinical trials of investigational therapies to eligible outpatients with COVID-19 so they can make informed decisions about participation (AIII).

### 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. 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 should be consulted about the risks and benefits that are 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.

Patients who use a continuous positive airway pressure (CPAP) device or a bilevel positive airway pressure (BiPAP) device to manage obstructive sleep apnea may continue to use their machine. As with nebulizers, patients should be advised to use the device only when they are isolated from others.

### References


