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COVID-19: Management of adults with acute illness in the outpatient setting

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INTRODUCTION

At the end of 2019, a novel coronavirus rapidly spread throughout the world, resulting in a global pandemic. The virus was designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the illness it caused coronavirus disease 2019 (COVID-19). The spectrum of COVID-19 in adults ranges from asymptomatic infection to mild respiratory tract symptoms to severe pneumonia with acute respiratory distress syndrome and multiorgan dysfunction. Our understanding of the spectrum of disease as well as optimal management strategies continues to evolve, particularly with the emergence of SARS-CoV-2 variants.

Recommendations on the outpatient management of patients with COVID-19 are provided by the World Health Organization, National Institute of Health COVID-19 Treatment Guidelines Panel in the United States, National Institute for Health and Care Excellence in the United Kingdom, and several academic medical centers [1-5].

This topic will address the management of adult patients with acute COVID-19 in the outpatient setting, including self-care advice, telehealth and outpatient management, and post-hospital discharge care. Data informing outpatient management strategies continue to evolve, and the approach described here is based upon a rapidly developing evidence base. In addition, clinicians should take into the account an individual patient's circumstances as well as available local resources when considering treatment options.

The evaluation and management of patients with persistent symptoms following recovery from acute viral infection is reviewed elsewhere. (See "COVID-19: Evaluation and management of adults with persistent symptoms following acute illness ("Long COVID")".)

Select topics reviewing the diagnosis and epidemiology and virology of COVID-19, the care of hospitalized patients, and considerations in special populations can be found elsewhere:

- (See "COVID-19: Epidemiology, virology, and prevention".)
- (See "COVID-19: Diagnosis".)
- (See "COVID-19: Clinical features".)
- (See "COVID-19: Management in hospitalized adults".)
- (See "COVID-19: Overview of pregnancy issues".)
- (See "COVID-19: Management in nursing homes".)

- (See "COVID-19: Vaccines".)
  (Related Pathway(s): COVID-19: Anticoagulation in adults with COVID-19.)

GENERAL PRINCIPLES

Outpatient management, including telehealth management, is appropriate for most patients with COVID-19. When possible, we favor a coordinated care management program that includes initial risk stratification, clinician telehealth visits, a dedicated outpatient respiratory clinic, and a close relationship with a local emergency department (ED). High-quality data supporting the superiority of any single outpatient management strategy are lacking. Our approach is based upon guidelines [6], as well as our own clinical experience of treating patients with COVID-19, and places additional emphasis on avoiding infection transmission, preserving limited resources, and reducing the burden on overwhelmed health care systems. These general principles are discussed in detail elsewhere. (See "COVID-19: Evaluation of adults with acute illness in the outpatient setting", section on 'General principles'.)

EVALUATION

The primary objective in evaluating an outpatient with suspected or confirmed COVID-19 is to assess the severity of symptoms, the risk of progression to severe disease (table 1), and the safety of the home setting to triage the appropriate site of care and to determine appropriateness of COVID-19-specific therapies. A detailed approach to the evaluation of outpatients with COVID-19 is discussed elsewhere. (See "COVID-19: Evaluation of adults with acute illness in the outpatient setting", section on 'Telephone triage'.)

TREATMENT WITH COVID-19-SPECIFIC THERAPIES

Indications for treatment — In the outpatient setting, we recommend treatment with COVID-19-specific therapy (algorithm 1) for symptomatic adults who have mild to moderate COVID-19 (ie, no hypoxia) **and** are at increased risk for progression to severe disease based on older age, immune status, COVID-19 vaccination history, and comorbidities associated with progression.

Specifically, we suggest COVID-19-specific therapy for symptomatic outpatients in the following categories:

- Adults ≥65 years old, regardless of vaccination status or other risk factors for severe disease. Those with multiple risk factors (table 1) are likely to benefit more from treatment than those without because their risk of severe disease may be higher. Nevertheless, advanced age alone is likely associated with a sufficiently high risk of progression to warrant COVID-19-specific therapy.

- Adults of any age who have a moderate to severe immunocompromising condition (table 2), regardless of vaccination status. These individuals may have suboptimal vaccine response. The expected benefit of treatment in such individuals is substantial.

- Adults of any age who have multiple risk factors for progression to severe disease (table 1), regardless of vaccination status.

- Adults ≥50 years old who are **not** vaccinated, regardless of risk factors. In particular, we recommend COVID-19-specific therapy for those who are completely unvaccinated and have no history of prior infection. Data on the

benefit of these therapies are most robust for unvaccinated populations.

Among the above, we are most likely to offer treatment to individuals with profound immunocompromise, with no history of vaccination or infection, or who are older with multiple comorbidities because these patients are at the highest risk and are most likely to achieve a substantial benefit from the treatment. Other people who meet the above criteria may also benefit from treatment, but their absolute risk of hospitalization and/or death is likely small even without treatment.

This approach is consistent with the indications outlined in the emergency use authorizations (EUAs) for available COVID-19-specific therapies (ie, mild to moderate COVID-19 and high risk of progression to severe disease). However, not all patients who meet the EUA eligibility criteria for COVID-19-specific therapy would derive clear benefit from it. In particular, among individuals who are up to date with COVID-19 vaccinations and have no medical comorbidities, the specific age threshold that should prompt treatment with COVID-19-specific therapy is uncertain. Although the Centers for Disease Control and Prevention identifies 50 years as the age threshold for increased risk of severe COVID-19, the risk of severe hospitalization and death does not steeply increase until after age 65 years and is especially high after age 75 [7,8].

Thus, we suggest against COVID-19-specific therapy for immunocompetent, healthy individuals ≤64 years who are up to date with recommended COVID-19 vaccinations and have one or no other risk factors for progression to severe disease (table 1). In such patients, the overall risk of progression to severe disease is so low that the absolute benefit of treatment does not outweigh any potential risk of harm (eg, medication adverse effects, potential drug-drug interactions, risk of "rebound COVID-19" requiring extension of the isolation period) [9].

Nevertheless, we engage **all** eligible patients in shared clinical decision-making regarding COVID-19-specific therapy, considering their individual risk factors as well as values and preferences. As an example, given the possibility of rebound COVID-19 following nirmatrelvir-ritonavir treatment, we would not treat solely to shorten the course of illness or the duration of the isolation period; the development of rebound COVID-19 would extend the duration of isolation. (See '"Rebound" COVID-19 after nirmatrelvir-ritonavir treatment' below.)

We also **do not** use COVID-19-specific therapy for individuals who have asymptomatic SARS-CoV-2 infection.

If a patient experiences severe side effects from COVID-19-specific therapy, the therapy can be stopped early if those side effects are thought to outweigh the expected benefits.

Treatment with COVID-19-specific therapies can be repeated with each new episode of infection.

Evidence supporting the benefit of COVID-19 specific therapy in different populations is discussed elsewhere. (See 'Efficacy and rationale' below and 'Alternative options' below.)

Patients with severe COVID-19 (ie, with hypoxia) generally warrant hospitalization; management of severe disease is discussed elsewhere. (See "COVID-19: Management in hospitalized adults", section on 'Approach'.)

Nirmatrelvir-ritonavir as preferred therapy — Nirmatrelvir-ritonavir, a combination of oral protease inhibitors, is our preferred option for COVID-19-specific therapy for symptomatic outpatients with risk for progression to severe disease. It substantially reduces the risk of hospitalization and mortality in some high-risk outpatients who have mild to moderate COVID-19 (ie, no hypoxia).

Nirmatrelvir blocks the activity of the SARS-CoV-2-3CL protease, an enzyme required for viral replication, and coadministration with ritonavir slows the metabolism of nirmatrelvir so it remains active in the body for longer and

at higher concentrations. The combination is expected to retain activity against Omicron and its subvariants [10].

Dose and administration — Nirmatrelvir-ritonavir should be initiated as soon as possible following COVID-19 diagnosis and within five days of symptom onset (with the first day of symptoms counting as day 1) (algorithm 1). We do not prescribe the medication unless a home or in-clinic test confirms the COVID-19 diagnosis as symptoms of COVID-19 overlap with other numerous respiratory viruses and the medication can cause side effects. In instances where a patient is at very high risk for hospitalization and severe disease (eg, tier 1) (table 3) and there may be a delay in receiving the results (eg, with polymerase chain reaction testing), providers may consider starting nirmatrelvir-ritonavir while results are pending and stop if the result is negative for SARS-CoV-2 infection.

The dose depends on the kidney function, and there are two different packaging configurations for the different doses:

- **For patients with normal kidney function (estimated glomerular filtration rate [eGFR] ≥60 mL/min)** – The dose is nirmatrelvir 300 mg-ritonavir 100 mg orally twice daily for five days. The dose pack contains two 150 mg nirmatrelvir tablets and one 100 mg ritonavir tablet to be taken together for each dose.
- **For patients with moderate kidney impairment (eGFR 30 to 59 mL/min)** – The dose is nirmatrelvir 150 mg-ritonavir 100 mg orally twice daily for five days. The dose pack contains one 150 mg nirmatrelvir tablet and one 100 mg ritonavir tablet to be taken together for each dose.

●**For patients with severe kidney impairment (eGFR <30 mL/min)** – The manufacturer does not recommend nirmatrelvir-ritonavir in patients with severe kidney impairment. However some experts suggest use with a reduced dose (ie, nirmatrelvir 300 mg-ritonavir 100 mg once on day one followed by nirmatrelvir 150 mg-ritonavir 100 mg once daily for the next four days) in such patients based on the pharmacokinetics, short duration, and limited observational data describing safe use [11-13]. Some experts suggest a further dose reduction in patients on dialysis who are <40 kg. (See "COVID-19: Issues related to end-stage kidney disease", section on 'Antiviral therapy'.)

For patients without a recent eGFR and in whom there is no suspicion for kidney impairment, it is reasonable to administer full-dose nirmatrelvir-ritonavir without checking a creatinine level.

Nirmatrelvir-ritonavir is also not recommended for patients with severe hepatic impairment (Child-Pugh class C) (table 4).

When prescribing nirmatrelvir-ritonavir, the numeric dose for each active ingredient should be specified (eg, nirmatrelvir-ritonavir 300 mg/100 mg, nirmatrelvir-ritonavir 150 mg/100 mg).

Although nirmatrelvir-ritonavir tablets are not approved to be chewed, broken, crushed, or administered via feeding tube, the manufacturer provides instructions about off-label administration via nasogastric tube, noting that off-label administration has not been tested or evaluated for pharmacokinetics/bioavailability, safety, or efficacy.

We give nirmatrelvir-ritonavir as monotherapy and do not combine it with other COVID-19-specific therapies. (See 'Alternative options' below.)

The use of nirmatrelvir-ritonavir during pregnancy is discussed elsewhere. (See "COVID-19: Antepartum care of pregnant patients with symptomatic infection", section on 'Use of antiviral therapy'.)

Drug interactions — Nirmatrelvir-ritonavir is both an inhibitor of metabolic enzymes and transporters such as the CYP3A enzyme (predominantly because of the ritonavir component) as well as a substrate of CYP3A [14,15].

Prior to prescribing nirmatrelvir-ritonavir, clinicians should both review the patient's prescribed medications, over-the-counter medications, and dietary supplements (including herbal preparations) and use a high-quality tool to assess specific drug interactions and potential ways to mitigate them. We recommend the:

- Drug interaction checker from the University of Liverpool
- Lexicomp drug interactions program included with UpToDate
- Drug interaction tables from the National Institute of Health
- US Food and Drug Administration Patient Eligibility Screening Checklist Tool

The approach to managing drug interactions depends on the type of interaction and whether the concomitant medication can be temporarily held or replaced:

- **CYP3A substrates** – For medications that are highly dependent on CYP3A for clearance and could be harmful at elevated levels, coadministration with nirmatrelvir-ritonavir is contraindicated [14]. Such medications include alfuzosin, amiodarone, colchicine, clozapine, lurasidone, lovastatin, rivaroxaban, salmeterol, simvastatin, and triazolam.

  However, if safe to do so, some of these medications (eg, statins) can be held while nirmatrelvir-ritonavir is administered. In some cases, reducing the dose of the concomitant medication with monitoring for potential adverse effects is a reasonable approach. Because the short course of nirmatrelvir-ritonavir is not expected to result in lasting inhibition of CYP3A, the concomitant medication (or the original dose) can be restarted at least three days after the five-day course has been completed; for older adult patients, in whom the inhibitory effect may persist for slightly longer, and for agents with very narrow therapeutic windows, it is reasonable to wait a longer period of time before restarting.

  However, the approach of stopping or dose reducing concomitant medications is not appropriate for medications that have a long half-life, such as amiodarone, as it would not mitigate the potential harm of the drug interaction; in such cases, an alternative COVID-19 therapy should be used.

- **CYP3A inducers** – For medications that are potent CYP3A inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort) (table 5), coadministration with nirmatrelvir-ritonavir is contraindicated because of the potential for reduced nirmatrelvir levels, loss of antiviral efficacy, and resistance. An alternative COVID-19 therapy should be used. Because the effect of these agents on CYP3A persists after discontinuation, temporarily holding them in order to administer nirmatrelvir-ritonavir would not mitigate the interaction and is not recommended.

Nirmatrelvir-ritonavir should **not** be dose adjusted to avoid potential drug interactions.

Although there is a concern that the use of nirmatrelvir-ritonavir in patients with uncontrolled HIV may select for HIV protease inhibitor resistance, we treat these patients with nirmatrelvir-ritonavir given the overwhelming benefit of treatment.

Efficacy and rationale — Support for the use of nirmatrelvir-ritonavir comes from several randomized trials and observational studies in symptomatic outpatients with COVID-19, which demonstrated reduction in hospitalization and death [8,16-22]. Although COVID-19-specific therapies have not been directly compared, outcomes data are more robust for nirmatrelvir-ritonavir than for the alternative options, and it is more practical than those alternatives that are given parenterally.

The clearest evidence of benefit with nirmatrelvir-ritonavir is among unvaccinated adults who are at risk for progression to severe disease. In the randomized EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) trial, which included 2246 unvaccinated adult outpatients with at least one risk factor for severe disease, administration of nirmatrelvir-ritonavir within three days of symptom onset reduced the risk of hospitalization or death at 28 days by 89 percent compared with placebo (0.7 versus 6.5 percent, risk difference -5.8, 95% CI -7.8 to -3.8) [16]. Results were similar when the drug was administered within five days of symptom onset. Further, all 13 trial deaths were COVID-19 related and occurred in the placebo group; there was no increase in drug-related adverse effects compared with placebo.

The benefits of nirmatrelvir-ritonavir are less certain for adults at lower risk for severe disease, such as those who have been vaccinated or who have had previous infection. In several large observational studies, nirmatrelvir-ritonavir has been associated with clinical benefit among vaccinated individuals who have underlying risk factors for severe disease [8,17,18,23,24]. As an example, in a study of 1130 vaccinated adults who received nirmatrelvir-ritonavir within five days of COVID-19 diagnosis and 1130 controls matched for age, gender, race, and comorbidities, nirmatrelvir-ritonavir was associated with a lower rate of emergency department (ED) visits, hospitalization, and death (odds ratio [OR] 0.5, CI 0.39-0.67) [23]. All 10 deaths were among those who had not been treated. In another observational matched cohort study of over 8000 high-risk patients with COVID-19 conducted in Quebec, Canada, nirmatrelvir-ritonavir was associated with reduced risk of hospitalization (relative risk [RR] 0.31, 95% CI 0.28-0.36), although the absolute risk reduction was 8 percent [25]. Furthermore, subgroup analysis showed that therapy only offered benefit to patients with an incomplete primary vaccination series and those who were severely immunocompromised or aged 70 years or older.

These observational studies were conducted during 2022, when Omicron subvariants were predominant, suggesting that nirmatrelvir-ritonavir retains efficacy against these variants. Subsequent in vitro data indicate that it is also active against newer subvariants [26].

However, data from observational studies must be interpreted with caution since there may be unmeasured variables (such as health literacy and social resources) that could impact both the likelihood of nirmatrelvir-ritonavir use and the clinical outcome. Trials have not conclusively demonstrated a benefit in vaccinated individuals or those at lower risk for severe disease. In an interim analysis of phase 2/3 of the unpublished EPIC-SR (Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients) trial, including 991 outpatients (unvaccinated adults without risk factors and vaccinated adults who have one or more risk factors for progression to severe disease), nirmatrelvir-ritonavir reduced the risk of hospitalization compared with placebo (0.7 versus 2.4 percent), although the difference did not achieve statistical significance [27]. There were no deaths in either trial group. Complete trial results are not available for review.

"Rebound" COVID-19 after nirmatrelvir-ritonavir treatment — "Rebound" of COVID-19 refers to recurrence of symptoms following initial improvement and/or increase in SARS-CoV-2 viral levels following initial decline (eg, as reflected by return to antigen positivity after having converted to negative antigen tests) within the first few weeks following infection. Increasing reports have described rebound following nirmatrelvir-ritonavir use. We advise patients of the possibility of rebound with nirmatrelvir-ritonavir, but for patients at risk for progression to severe disease (such as those with advanced age or multiple comorbidities), the potential benefits of treatment greatly outweigh any potential inconvenience from rebound. By contrast, we do not use nirmatrelvir-ritonavir simply to shorten the duration of viral shedding in people who are not at high risk for progression, as the possibility of rebound negates this effect. (See 'Indications for treatment' above.)

- **Incidence and clinical significance** – The precise frequency of viral or symptom rebound following nirmatrelvir-ritonavir is uncertain. Some studies have reported rates of approximately 1 to 2 percent [28-30]. However, in our clinical experience and in other studies, the apparent rate of viral rebound with repeat antigen positivity is somewhat higher (possibly closer to 5 to 15 percent), and many of those patients have mild recurrent symptoms [31]. In studies, most episodes of rebound occur within the first 10 days of stopping nirmatrelvir-ritonavir [28,32]. Viral and symptom rebound has also been described following infection in people who have not received antiviral therapy [29,33], although preliminary data suggest that the peak viral levels are higher with rebound after nirmatrelvir-ritonavir [34].

  Rebound has been described in both vaccinated and unvaccinated patients. Recurrent symptoms are generally mild (often cold-like symptoms) [28,29,32], although more severe complications have been rarely reported [35].

- **Management of rebound** – Patients who have recurrent symptoms following nirmatrelvir-ritonavir treatment should undergo antigen testing. We advise those who have a repeat positive antigen test to restart the isolation period (algorithm 2). Isolation guidance is discussed in detail elsewhere. (See "COVID-19: Infection prevention for persons with SARS-CoV-2 infection", section on 'Isolation at home'.)

  Consistent with Centers for Disease Control and Prevention guidance, given the mild nature of most rebound episodes, we do not routinely retreat patients with nirmatrelvir-ritonavir (or any other COVID-19-specific therapy) in such circumstances [36]. However, for select patients with significant immunosuppression (eg, solid organ and hematopoietic transplant patients; individuals with advanced HIV infection) and rebound COVID-19, some experts offer retreatment with a five-day course of nirmatrelvir-ritonavir, although there is a lack of high-quality evidence to support this approach.

Research is ongoing to determine the implications of recurrent symptoms and/or return of antigen positivity on rapid testing several days after completion of therapy.

Alternative options

Selecting among alternative options — If nirmatrelvir-ritonavir is not available or appropriate, potential alternative options include remdesivir and convalescent plasma (algorithm 1). Although the antiviral agent molnupiravir has an EUA for mild to moderate symptomatic COVID-19 in patients at risk for progression and is recommended by some guidelines (eg, National Institute of Health), we do not use it, because the benefit is unproven and studies do not consistently demonstrate efficacy against hospitalization or death (see 'Therapies of limited or uncertain benefit' below). Previously, monoclonal antibodies (eg, bebtelovimab) were also an option; however, they are not active against increasingly prevalent new Omicron variants worldwide (eg, BQ1.1). We do not combine therapies for outpatients and only select one from the options.

We use remdesivir as our preferred alternative option. Remdesivir reduces COVID-19-associated hospitalization but requires three intravenous (IV) doses over three days and thus may be operationally challenging to administer. Among outpatients, remdesivir may be best suited for those residing in institutional settings, such as skilled nursing facilities. Administration through infusion centers may also help improve access. (See 'Remdesivir' below.)

If nirmatrelvir-ritonavir or remdesivir is not available or appropriate, high-titer convalescent plasma is a potential option. However, although it can reduce COVID-19-associated hospitalization, high-titer convalescent plasma requires processes for collection, screening, and quantification and may not be widely available. The use of low-titer convalescent plasma is not appropriate or authorized per the EUA [37]. (See 'High-titer convalescent plasma' below.)

An additional practical consideration when selecting an alternative regimen is that the resources and infrastructure required for administration of the parenteral options (remdesivir, high-titer convalescent plasma) may divert resources from other COVID-19 care efforts and may favor use in resource-rich over resource-limited communities [38]. It is essential that equitable access to all COVID-19 treatments be ensured.

Selection of COVID-19-specific therapy in pregnancy is largely the same as in nonpregnant adults and is reviewed in detail elsewhere. (See "COVID-19: Antepartum care of pregnant patients with symptomatic infection", section on 'Use of antiviral therapy'.)

Remdesivir — For symptomatic outpatients who are at risk of severe disease (table 1) and cannot use nirmatrelvir-ritonavir, remdesivir, a nucleotide analog that inhibits the SARS-CoV-2 RNA polymerase, is our preferred alternative option for COVID-19-specific therapy. Remdesivir reduces the risk of hospitalization in such patients. However, it requires parenteral administration over three days, which makes administration operationally complicated in many outpatient settings. Remdesivir may be most feasible for those residing in institutional settings, such as skilled nursing facilities, or for hospitalized patients with "incidental" (not the reason for hospitalization), nonsevere COVID-19.

Remdesivir is administered as 200 mg IV on day 1, followed by 100 mg IV daily on days 2 and 3. This dosing is distinct from that used for patients hospitalized for COVID-19. It should be initiated as soon as possible following COVID-19 diagnosis and within seven days of symptom onset (algorithm 1).

In a randomized controlled trial of 562 unvaccinated outpatients (≥12 years of age with at least one risk factor for progression to severe disease or ≥60 years of age) with mild to moderate COVID-19 (ie, no hypoxia), initiation of a three-day course of IV remdesivir (200 mg on day one and 100 mg on days two and three) within seven days of symptom onset reduced the risk of COVID-19 related hospitalization by 87 percent compared with placebo (HR 0.13, 95% CI 0.03-0.59) [39]. The risk of all-cause hospitalization was also lower with remdesivir (HR 0.28, 95% CI 0.10-0.75). At day 28, there were no deaths recorded in either study group. Although these data cannot inform the impact of remdesivir on mortality, a reduction in hospitalization remains a patient-important outcome as well as an important consideration for overwhelmed health care systems.

In the trial, adverse effects were reported to be minimal and similar to placebo, although nausea, bradycardia, hypotension, and hypersensitivity reactions have been reported following administration of remdesivir [40-42]. This is discussed elsewhere.

A newer oral formulation of remdesivir has completed a phase III trial successfully, demonstrating similar time to sustained clinical recovery compared with nirmatrelvir-ritonavir [43].

High-titer convalescent plasma — We consider high-titer convalescent plasma an alternative option for COVID-19-specific therapy for symptomatic outpatients (especially those who are immunocompromised) with risk for progression to severe disease (table 1) if nirmatrelvir-ritonavir or remdesivir are not available or appropriate [44]. Some data suggest a clinical benefit, but this approach requires a process to collect, screen, and verify convalescent plasma as high-titer, which may not be widely available.

If given, high-titer convalescent plasma should be administered as soon as possible following COVID-19 diagnosis; experts suggest administering it as early as possible and at the latest within eight days of symptom onset (algorithm 1) [45]. High-titer convalescent plasma can also be considered later in the disease course in immunocompromised patients who have continued viremia and are not improving symptomatically. In vitro studies show that high-titer convalescent plasma collected from individuals who have recovered from infection with strains

other than Delta and Omicron has virus-neutralizing capability against Omicron (as well as earlier variants), despite a lack of exposure [46]. Convalescent plasma not verified as having a high-titer should not be used. The collection, preparation, administration, and adverse effects of convalescent plasma are discussed in detail elsewhere. (See "COVID-19: Convalescent plasma and hyperimmune globulin".)

High-quality trials suggest that high-titer convalescent plasma may reduce the risk of progression to severe disease and reduce hospitalization in selected outpatients without severe disease [44,47,48], although not all trials in this population have demonstrated a benefit [49-51]. The reasons for the differences in these trials may be related to differences in the study population (eg, disease severity at presentation) and/or titer of plasma used. Of note, the titer thresholds used to define "high-titer" plasma cannot be compared across trials, as they used different assays and titer measurement is not standardized across assays.

In a meta-analysis of five randomized controlled trials that included over 2600 patients, administration of convalescent plasma had a lower rate of hospitalization compared with placebo (8.5 versus 12.2 percent; absolute risk reduction 3.7, 95% CI 1.3-6.0) [52]. Those who received the convalescent plasma within five days of symptoms or received high-titer (≥median neutralization titer for each study) convalescent plasma had an even greater reduction in hospitalization. In one of the randomized trials included in the meta-analysis, of 1181 adults with nonsevere COVID-19, including some individuals who had been vaccinated, administration of high-titer (>1:320) convalescent plasma within nine days of symptom onset reduced the risk of COVID-19-associated hospitalization compared with control plasma (6.3 to 2.9 percent; absolute risk reduction 3.4, 95% CI 1.0-5.8) but did not lead to faster resolution of symptoms [48,51].

However, another placebo-controlled trial (also included in the meta-analysis mentioned above) that included 511 high-risk adults who were seen in an ED for COVID-19 and deemed appropriate for outpatient management failed to identify a clinical benefit of high-titer convalescent plasma (≥1:250; median 1:650) administered within seven days of symptom onset [49].

Among many of the trials, the overall mortality rate was too low to make a precise estimate about the impact of convalescent plasma [45].

While other guidelines do not universally recommend convalescent plasma, because of the lack of consistent trial results [53], some members of the National Institutes of Health (NIH) guidelines panel choose to administer convalescent plasma to select immunocompromised patients because of the potential benefit seen in subgroup analyses [54].

Therapies of limited or uncertain benefit

- **Molnupiravir** – Molnupiravir is a nucleoside analog that inhibits SARS-CoV-2 replication. Although it reduces the time to recovery, studies do not demonstrate efficacy against hospitalization or death. Therefore, we do not recommend molnupiravir as an alternative treatment.

  The NIH guidelines continue to offer molnupiravir as an alternative option for those who cannot receive nirmatrelvir-ritonavir and remdesivir. If used, the dose is 800 mg (four 200 mg capsules) taken orally every 12 hours for five days. It should be initiated as soon as possible following COVID-19 diagnosis and within five days of symptom onset (algorithm 1) [55]. No dose adjustment is necessary based upon kidney or hepatic impairment. Molnupiravir is contraindicated for use in patients younger than 18 years due to bone and cartilage toxicity. It is also not recommended during pregnancy and lactation; although there are no human pregnancy data, animal studies demonstrate fetal developmental abnormalities with molnupiravir exposure.

Use in individuals of childbearing potential should be avoided unless no other treatment alternatives are available (see "COVID-19: Antepartum care of pregnant patients with symptomatic infection", section on 'COVID-19-specific treatments'). If used, prior to initiating molnupiravir, the possibility of pregnancy should be assessed. In females of childbearing potential, a pregnancy test is recommended if they have irregular menstrual cycles, are unsure of the first day of their last menstrual cycle, or are not consistently using effective contraception. Females are advised to use reliable contraception during and for four days following therapy. Males who are sexually active with females of childbearing potential should use a reliable method of contraception consistently during and for at least three months following therapy. There are no medications that are contraindicated for coadministration with molnupiravir.

Although the evidence for molnupiravir is conflicting, any potential benefit is likely modest [56-61]. In a randomized, open-label trial of over 25,000 nonhospitalized adults with onset of mild COVID-19 infection within five days and with at least one risk factor for severe disease, molnupiravir did not reduce the risk of hospitalization or death (1 versus 1 percent, adjusted OR 1.06) but did reduce the time to recovery (9 versus 15 days, HR 1.36, 95% CI 1.3-1.4) [56]. These findings contrast with lower-quality data that suggested a possible reduction in severe disease with molnupiravir. As an example, in an international randomized controlled trial including 1433 nonhospitalized, unvaccinated adults who had onset of mild to moderate COVID-19 (ie, no hypoxia) within five days and at least one risk factor for severe disease, molnupiravir reduced the risk of hospitalization or death by approximately 31 percent (HR 0.69, 95% CI 0.48-1.01); the combined outcome occurred in 6.8 versus 9.7 percent of patients compared with placebo, which trended toward but did not achieve statistical significance [57]. Of the 10 deaths reported among trial participants, one occurred in the molnupiravir group and nine occurred in the placebo group. The rates of drug-related adverse events were comparable between the two groups. Similarly, in an observational study of over one million patients with COVID-19, molnupiravir use was associated with lower risk of death (HR 0.76, 95% CI 0.61-0.95) compared with nonuse, although risk of hospitalization was similar between the two groups [58]. Although this study was large, its observational nature does not allow it to control for all confounding factors.

- **Inhaled glucocorticoids** – Evidence regarding the benefits of inhaled glucocorticoids is mixed, and we agree with the Infectious Diseases Society of America that COVID-19 should not be treated with inhaled corticosteroids outside of a clinical trial [62].

  A 2022 systematic review including three trials concluded with moderate certainty that inhaled corticosteroids reduce the risk of hospitalization in unvaccinated patients [63]. However, while the two smaller included trials suggested a reduction in ED evaluation and hospital admission, the largest trial, which included outpatients at risk for severe disease, did not. Some of the trials were open-label design, which reduces confidence in the findings, and no trials identified a mortality benefit. As examples:

  - In the non-placebo-controlled steroids in COVID-19 (STOIC) trial, 139 adult outpatients with mild, early COVID-19 were treated with inhaled budesonide 800 mcg twice daily (an average of seven days) or assigned to usual care [64]. Among those treated with inhaled budesonide, fewer patients required urgent medical evaluation or hospitalization (1 versus 14 percent) at 28 days.

  - In an open-label trial (the PRINCIPLE trial) including 1856 COVID-19 outpatients ≥65 years old or ≥50 years old with risk factors for severe disease, treatment with inhaled budesonide 800 mcg twice daily did not reduce the risk of hospitalization or death at 28 days compared with usual care [65]. However, the use of a self-reported outcome in an open-label trial, inclusion of participants with presumed but not confirmed

COVID-19, and enrollment of the usual care group over a longer period of time than the intervention group all increase the risk of bias and reduce confidence in the finding of a potential benefit of budesonide.

- In a randomized controlled trial including 400 adults and children aged ≥12 with nonsevere COVID-19, treatment with inhaled ciclesonide (320 mcg twice daily for 30 days) initiated within 72 hours of a positive SARS-CoV-2 test reduced the combined outcome of ED visit or hospital admission within 30 days compared with placebo (1 versus 5.4 percent; OR 0.18, 95% CI 0.04-0.85) [66]. However, there was no reduction in the sole outcome of hospital admissions; no deaths occurred in either study group.

Despite a suggestion of benefit, additional high-quality randomized controlled trials are necessary to determine the efficacy of inhaled corticosteroids for outpatients with early, nonsevere COVID-19. A subsequent, unpublished double-blind randomized trial that included nearly 1300 patients with symptomatic nonsevere COVID-19 did not identify reduced time to recovery or hospitalization rates with inhaled fluticasone compared with placebo; approximately 65 percent had received at least two vaccine doses and many participants did not have risk factors for disease progression [67].

- **Monoclonal antibodies** – Anti-SARS-CoV-2 monoclonal antibodies used to be alternative options for COVID-19-specific therapy [68-70]. However, monoclonal antibodies have variable activity against the different SARS-CoV-2 variants, and there are no monoclonal antibodies with activity against the increasingly prevalent Omicron sublineages BQ.1 and BQ1.1 in the United States (table 6). Thus, bebtelovimab is no longer authorized for use to treat COVID-19 in the United States [71]. In settings with high prevalence of SARS-CoV-2 variants that are susceptible to monoclonal antibodies, monoclonal antibodies can still be considered a reasonable alternative option.

  Bebtelovimab is the only available monoclonal antibody that is active against previously circulating Omicron sublineages (including BA.5, BF.7, and BA.4.6) (table 6). Bebtelovimab is administered as a single 175 mg IV dose as soon as possible after diagnosis and within seven days of symptom onset (algorithm 1). Data to support its use are limited mainly to an unpublished trial among low-risk outpatients, in which bebtelovimab reduced the time to sustained symptom resolution to six days from eight days with placebo. The risk of COVID-19-associated hospitalization and death was similarly low with bebtelovimab and placebo (1.6 percent) [72]. Use of bebtelovimab against susceptible variants is further supported by randomized controlled trials showing reduction in hospitalization rates with other monoclonal antibody therapies (eg, sotrovimab, casirivimab-imdevimab, bamlanivimab-etesevimab), which are no longer used, because they are ineffective against circulating variants [69,73-78].

- **Pegylated interferon lambda** – Early evidence regarding the benefits of pegylated interferon lambda is promising, but it is not available for treatment. In a randomized, controlled study of almost 2000 mostly vaccinated patients with symptomatic mild to moderate COVID-19 illness and at least one risk factor for severe disease, one dose of pegylated interferon lambda (180 micrograms) administered within seven days of symptom onset was associated with a lower rate of COVID-19 related hospitalization compared with placebo (2.3 versus 3.9 percent; RR 0.58, 95% CI 0.34-0.96) [79]. Rates of adverse events were similar between the two groups (15 versus 17 percent). By contrast, other smaller randomized controlled trials did not show a difference in hospitalization rates between interferon-treated and placebo groups but may not have been powered to detect a difference [80,81].

Therapies that we do not recommend — Other COVID-19 treatments are under investigation but should not be prescribed in the ambulatory setting outside of a clinical trial, as high-quality data supporting the efficacy of these

treatments are lacking [82,83]. In addition, there are concerns for potential toxicities with some of these agents when administered in an unmonitored setting [84,85]. (See "COVID-19: Management in hospitalized adults", section on 'Specific treatments'.)

- **Hydroxychloroquine and azithromycin** – Hydroxychloroquine and azithromycin have received attention as agents with possible antiviral activity, but trials have not suggested a clinical benefit for patients with COVID-19, including those managed in the outpatient setting [86-91]. Although some observational and unpublished anecdotal reports have suggested a clinical benefit of hydroxychloroquine, those are subject to a number of potential confounders [92], and randomized trials offer higher-quality evidence that hydroxychloroquine has no proven role for COVID-19. As an example, in an open-label trial including 293 patients with mild COVID-19 who did not warrant hospitalization, hydroxychloroquine administered within five days of symptom onset did not reduce viral levels at day 3 or 7 compared with no treatment, and there was no statistically significant reduction in hospitalization rates or time to symptom resolution [86]. The rate of adverse effects, primarily gastrointestinal symptoms, were greater with hydroxychloroquine.

- **Ivermectin** – High-quality data suggest that ivermectin is ineffective for the treatment of COVID-19 and should not be used for this indication [93]. Several meta-analyses including earlier trials have highlighted that the efficacy of ivermectin remained uncertain because of a lack of high-quality data, including imprecision and risk of bias [94-97]. However, in subsequent high-quality trials, lack of efficacy has been confirmed [98-102]. As an example, in a randomized trial including 1358 adults outpatients with nonsevere COVID-19 and at least one risk factor for progression to severe disease, treatment with ivermectin (400 mcg/kg orally once daily for three days) within seven days of symptom onset did not reduce the risk of ED visit or hospitalization at 28 days compared with placebo [98].

  Of note, steep increases in calls to poison control centers about ivermectin toxicity compared with pre-pandemic rates have been reported [103,104]. Several of these calls involved ivermectin obtained without prescription (eg, from internet or veterinary sources); some patients were hospitalized for neurologic adverse effects related to uncertain dosages.

- **Fluvoxamine** – There is insufficient evidence supporting the use of fluvoxamine, and it should not be used to treat COVID-19 outside a clinical trial. Early limited data suggested that the antidepressant fluvoxamine may reduce progression to severe disease in early, mild COVID-19. However, trials indicating benefit are hampered by methodologic issues, reducing certainty about any effect [105]. Higher-quality randomized controlled trials have failed to demonstrate a benefit [100,106,107]. As an example, in a trial of 1331 participants, the median time to sustained recovery (13 versus 12 days) and number of hospitalizations (one versus two hospitalizations) both appeared similar between the fluvoxamine (50 mg twice daily for 10 days) and placebo groups [107]. In another randomized trial from Brazil including 1497 outpatients, fluvoxamine (100 mg twice daily for 10 days) reduced the 28-day rate of hospitalization compared with placebo (11 versus 16 percent, RR 0.68, 95% CI 0.52-0.88), although most of the reduction in "hospitalizations" reflected a reduction in ED visits rather than inpatient admissions [106]. A mortality reduction was only observed among those who reported at least 80 percent adherence to the study medication (<1 versus 2 percent with placebo, RR 0.09, 0.01-0.47). However, the validity of this finding is uncertain because more individuals in the fluvoxamine than the placebo group were nonadherent; the resulting mortality rate among those who were nonadherent was disproportionately high compared with the overall rate, suggesting potential confounders.

- **Colchicine** – Although there are some data demonstrating a benefit from the use of colchicine in early nonsevere COVID-19, the benefit is modest, there is no reduction in mortality, and adverse effects are

common.

In a randomized trial including over 4100 adult outpatients (≥age 40) with early COVID-19, treatment with oral colchicine (0.5 mg twice daily for three days, followed by 0.5 mg daily for a total of 30 days), initiated within one day of diagnosis, reduced the risk of hospitalization compared with placebo (4.5 versus 5.9 percent of patients; OR 0.75, 95% CI 0.57-0.99); there was no reduction in mortality [108]. Gastrointestinal side effects (eg, diarrhea) were more common, and pulmonary embolism occurred more frequently in the colchicine compared with the placebo group (24 versus 15 percent; and 0.5 versus 0.1 percent, respectively). Another randomized controlled trial of over 1900 adult outpatients (≥age 30) showed similar results [109].

- **Systemic glucocorticoids in outpatients** – In nonhospitalized patients, we do not treat COVID-19 with dexamethasone, prednisone, or other corticosteroids [110,111]. Extrapolating from the results of studies of hospitalized patients, there is no evidence that corticosteroids benefit patients without a supplemental oxygen requirement, and further, they may be associated with poorer clinical outcomes [112,113]. However, in resource-limited settings with limited hospital capacity, it may be reasonable to treat select COVID-19 outpatients who have a new or increased supplemental oxygen requirement with dexamethasone if close clinical follow-up can be assured [114]. In addition, patients with COVID-19 and a concomitant acute exacerbation of asthma or chronic obstructive pulmonary disease should receive appropriate treatment with systemic glucocorticoids as indicated by usual guidelines. This is reviewed in detail elsewhere. (See "An overview of asthma management", section on 'Advice related to COVID-19 pandemic' and "Stable COPD: Overview of management", section on 'Advice related to COVID-19'.)

  Use of glucocorticoids for hospitalized patients with COVID-19 is discussed in detail elsewhere. (See "COVID-19: Management in hospitalized adults", section on 'Dexamethasone and other glucocorticoids'.)

- **Antibiotics** – For patients with documented COVID-19, treatment with antibiotics is not indicated [114,115]. Data are limited, but bacterial superinfection does not appear to be a prominent feature of COVID-19. Treatment for bacterial pneumonia may be reasonable if the diagnosis is uncertain, or in patients with documented COVID-19 in whom there is clinical suspicion (eg, new fever after defervescence with new consolidation on chest imaging). (See "COVID-19: Management in hospitalized adults" and "COVID-19: Management in hospitalized adults", section on 'Empiric treatment for bacterial pneumonia in selected patients'.)

- **Anticoagulation/antiplatelet therapy** – Outpatients with COVID-19 who are already receiving anticoagulant or antiplatelet therapy for underlying conditions should continue these medications. However, we do not initiate anticoagulation or antiplatelet therapy unless the patient has specific indications for treatment or is participating in a clinical trial [109,116]. Consultation with an appropriate specialist (eg, hematology, pulmonology) may be helpful in circumstances where anticoagulation is being considered. (See "COVID-19: Hypercoagulability", section on 'Patients not admitted to the hospital'.)

- **Metformin** – The available data have not shown metformin to be effective in reducing the risk to severe progression in patients with mild to moderate COVID-19. As an example, in one randomized controlled trial of over 400 unvaccinated nonhospitalized patients with recent (≤7 days of symptoms) COVID-19 infection and increased risk of progressing to severe disease, there was no improvement in viral clearance, clinical improvement, or time to hospitalization or death in those who received extended-release metformin 750 mg compared with placebo [117]. The study was stopped early for futility. In another randomized controlled trial of

over 1000 nonhospitalized symptomatic patients with COVID-19, immediate-release metformin 1500 mg was not associated with decreased risk of hypoxemia, an ED visit, hospitalization, or death [100].

- **Others** – Other treatments are being evaluated in outpatients with nonsevere illness, including vitamin and mineral supplementation, metformin, as well as antiviral agents and anticoagulants.

  - Although limited observational data suggest a possible association between certain vitamin and mineral deficiencies and more severe disease [118-121], there are limited high-quality data that supplementation with vitamin C, vitamin D, or zinc reduces the severity of COVID-19 in nonhospitalized patients [122]. Zinc may reduce symptom duration in patients with mild COVID-19 [123]. Issues related to vitamin D and COVID-19 are reviewed in detail elsewhere. (See "Vitamin D and extraskeletal health", section on 'COVID-19'.)

  - There is no evidence that treatment with lopinavir-ritonavir improves outcomes in outpatients with mild disease [89]. In addition, although treatment with peginterferon lambda may induce more rapid reduction in SARS-CoV-2 viral load in patients with early, mild disease, its impact on clinically important outcomes is unclear [81].

  - In a randomized trial including 243 adults with mild to moderate COVID-19 (ie, no hypoxia) but risk factors for progression to severe disease, treatment with sulodexide (a glycosaminoglycan with anticoagulant and antiinflammatory properties) within three days of symptom onset reduced hospitalizations and the need for supplemental oxygen compared with placebo (RR 0.60, 95% CI 0.37-0.96 and RR 0.71, 95% CI 0.50-1.00, respectively), but not mortality or thromboembolic events [124]. Further trials are required to determine if there is a clinical role for this agent in treating outpatients with COVID-19.

Clinicians may refer patients for participation in available clinical trials of investigational COVID-19 therapies. A catalog of clinical trials can be found at covid-trials.org; the list of trials can be filtered by location, type of study, patient setting (ie, outpatient versus inpatient), and many other criteria.

Other COVID-19-specific therapies are being used to treat hospitalized patients; these therapies are discussed in detail elsewhere. (See "COVID-19: Management in hospitalized adults", section on 'COVID-19-specific therapy'.)

COUNSELING ON ISOLATION AND PREVENTING SPREAD OF INFECTION

With all patients, we reinforce the importance of infection control and self-isolation and provide instructions on the anticipated duration of isolation (algorithm 2). These are reviewed in detail elsewhere. (See "COVID-19: Infection prevention for persons with SARS-CoV-2 infection", section on 'Infection prevention in the home setting'.)

OTHER MANAGEMENT ISSUES

Symptom management and recovery expectation — Symptomatic treatment includes antipyretics and analgesics for fever, myalgias, and headaches. We generally prefer acetaminophen; however, we inform patients that nonsteroidal antiinflammatory drug (NSAID) use is acceptable if symptoms do not respond to acetaminophen. (See "COVID-19: Management in hospitalized adults", section on 'NSAID use'.)

All other care is generally supportive, similar to that advised for other acute viral illnesses:

- We advise that patients stay well hydrated, particularly those patients with sustained or higher fevers, in whom insensible fluid losses may be significant.

- Cough that is persistent, interferes with sleep, or causes discomfort can be managed with an over-the-counter cough medication (eg, dextromethorphan) or prescription benzonatate, 100 to 200 mg orally three times daily as needed.

- We advise rest as needed during the acute illness; for patients without hypoxia, frequent repositioning and ambulation is encouraged. In addition, we encourage all patients to advance activity as soon as tolerated during recovery.

- Patients are cautioned that progressive respiratory symptoms, particularly worsening dyspnea, should prompt contact with their clinician for further evaluation. (See "COVID-19: Evaluation of adults with acute illness in the outpatient setting", section on 'Reevaluation for worsening clinical acuity'.)

In addition, we educate patients about the wide variability in time to symptom resolution and complete recovery from COVID-19. Although early data from China suggested that unvaccinated patients with mild disease recovered in two weeks and those with more severe disease recovered in three to six weeks [125], accumulating data suggest that the course of recovery is more variable and may depend upon a variety of contributors including host factors (eg, age, health status), illness severity [126], SARS-CoV-2 variant, and vaccination status. In our experience, most patients recover within two weeks; however, a substantial minority have symptoms that gradually resolve over a longer period of time, usually two to three months. Evaluation and management of patients who have symptoms that persist beyond three months is discussed elsewhere. (See "COVID-19: Clinical features", section on 'Recovery and long-term sequelae' and "COVID-19: Evaluation and management of adults with persistent symptoms following acute illness ("Long COVID")".)

Management of chronic medications — In general, the patient's usual home medication regimen is not adjusted, although some changes may be needed.

In patients who are taking nirmatrelvir-ritonavir for COVID-19 therapy, chronic medications may need to be temporarily adjusted because of drug interactions. (See 'Nirmatrelvir-ritonavir as preferred therapy' above.)

Additionally, we advise patients who use nebulized medications to avoid their use in the presence of others and to use a metered dose inhaler preparation instead, when possible, to avoid potential aerosolization of SARS-CoV-2. (See "COVID-19: Management in hospitalized adults", section on 'Nebulized medications' and "COVID-19: Respiratory care of the nonintubated hypoxemic adult (supplemental oxygen, noninvasive ventilation, and intubation)", section on 'Nebulized medications'.)

If patients already use a continuous positive airway pressure or bilevel positive airway pressure device for management of obstructive sleep apnea, they may continue to use their machine; as with nebulizers, they are advised to use the device only when isolated from others.

For patients taking an immunomodulating medication, we consult with the prescribing clinician about the relative risks and benefits of temporarily discontinuing it, which depend upon its indication and the severity of the underlying condition. (See "COVID-19: Issues related to solid organ transplantation", section on 'Adjusting immunosuppression' and "COVID-19: Care of adult patients with systemic rheumatic disease", section on 'Medication management with documented or presumptive COVID-19' and "COVID-19: Issues related to

gastrointestinal disease in adults", section on 'Adjusting IBD medications' and "COVID-19: Considerations in patients with cancer".)

Outpatients with COVID-19 who are already receiving anticoagulant or antiplatelet therapy for underlying conditions should continue these medications. (See "COVID-19: Hypercoagulability", section on 'Patients not admitted to the hospital'.)

Management of medications is reviewed in more detail elsewhere. (See "COVID-19: Management in hospitalized adults", section on 'Managing chronic medications' and "COVID-19: Management in hospitalized adults", section on 'NSAID use' and "COVID-19: Management in hospitalized adults", section on 'Nebulized medications' and "COVID-19: Management in hospitalized adults", section on 'Immunomodulatory agents' and "COVID-19: Issues related to acute kidney injury, glomerular disease, and hypertension", section on 'Renin angiotensin system inhibitors' and "Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus", section on 'Immune function' and "COVID-19: Issues related to diabetes mellitus in adults".)

Counseling on warning symptoms — We counsel all patients on the warning symptoms that should prompt reevaluation by telehealth visit and in-person, including emergency department (ED) evaluations. These include new onset of dyspnea, worsening dyspnea, dizziness, and mental status changes such as confusion. Patients with obstructive lung disease (eg, chronic obstructive pulmonary disease or asthma) are specifically advised to closely monitor their respiratory status and are cautioned not to presume that any worsening shortness of breath is due to an exacerbation of their underlying lung disease. All patients who develop worsening dyspnea require further evaluation. (See "COVID-19: Evaluation of adults with acute illness in the outpatient setting", section on 'Reevaluation for worsening clinical acuity'.)

Persistent infection in immunocompromised patients — Active, persistent SARS-CoV-2 infection can occur in immunocompromised patients, particularly those with severe B-cell depletion (eg, on rituximab or following hematopoietic cell transplantation). In such cases, patients typically test positive for SARS CoV-2 on reverse-transcriptase polymerase chain reaction for prolonged periods of time (weeks to months) with a low cycle threshold (which suggests a high viral RNA level). Genomic studies have distinguished such persistent infection from reinfection with prevalent variants by the pattern of viral evolution [127].

Data to guide the optimal management of these patients are limited, and clinical practice is variable. Persistent infection can often be difficult to treat due to the accelerated pace of viral evolution and development of escape mutations [128-131]. Potential options for individuals with symptomatic persistent infection despite initial treatment (see 'Treatment with COVID-19-specific therapies' above) that have been posed by members of the NIH COVID-19 treatment guidelines panel include prolonged or repeated courses of nirmatrelvir-ritonavir or remdesivir, or high-titer convalescent plasma (eg, from an individual with a recent infection with the same variant as in the immunocompromised patient) [54]. Case series have also reported cure of infection with combinations of antiviral therapy (eg, nirmatrelvir-ritonavir and/or remdesivir) and antibody-based therapies (eg, high-titer convalescent plasma or active monoclonal antibodies) [128,132-136].

Clinicians may have difficulties obtaining a prolonged course of nirmatrelvir-ritonavir for patients given the duration proscribed in the original authorization; if needed, clinicians can try to obtain the medication through an expanded access program by contacting the manufacturer.

Persistent infection in immunocompromised patients is a distinct issue from "long COVID-19," which is characterized by prolonged symptoms despite no evidence of ongoing infection, does not warrant repeat antiviral treatment, and

is discussed in detail elsewhere. (See "COVID-19: Evaluation and management of adults with persistent symptoms following acute illness ("Long COVID")".)

COVID-19 vaccination after recovery from acute illness — Advice on COVID-19 vaccination after recovery from acute infection, including individuals who received monoclonal antibody treatment is reviewed in detail elsewhere. (See "COVID-19: Vaccines", section on 'History of SARS-CoV-2 infection'.)

POST-DISCHARGE MANAGEMENT

After discharge from the inpatient hospital setting or the emergency department (ED), clinician follow-up is usually warranted, either in outpatient clinic or via telehealth visit [137]. At each encounter, we provide counseling on the warning symptoms which should prompt reevaluation. (See "COVID-19: Evaluation of adults with acute illness in the outpatient setting", section on 'Counseling' and 'Counseling on isolation and preventing spread of infection' above.)

In some cases, patients are discharged home or to supervised residential care from the inpatient hospital setting on low flow oxygen therapy, with oximetry monitoring by telehealth (preferred if available) or visiting nurse. The practice of sending patients home on supplemental oxygen is widely variable, however, and if done warrants careful patient selection and close monitoring [138]. In general, COVID-19-specific therapies initiated in the hospital (eg, dexamethasone, remdesivir, baricitinib) should not be continued after discharge [114].

Some patients discharged from the hospital, including those with documented venous thromboembolism as well as some who are at high risk for venous thromboembolism, will be discharged on anticoagulation. Management of anticoagulation is discussed in detail elsewhere. (See "COVID-19: Hypercoagulability", section on 'Patients discharged from the hospital'.) (Related Pathway(s): COVID-19: Anticoagulation in adults with COVID-19.)

Patients discharged home

- Patients discharged from the inpatient setting usually require a follow-up clinician visit following discharge; depending upon their clinical and social situation, telehealth visit [139] or in-person visit may be appropriate.
- For patients evaluated and discharged from the ED who are felt to need follow-up care, telehealth visits may also be appropriate. The timing of such visits will vary depending upon patient acuity and indication.

Patients discharged to supervised residential care for recovery — As part of the continuum of care of patients with COVID-19, temporary housing in supervised residential care facilities may also be appropriate for patients discharged from the ED. (See "COVID-19: Evaluation of adults with acute illness in the outpatient setting", section on 'Assess home setting and social factors'.)

Depending upon the type of facility, the patient's medical acuity, and available resources, telehealth follow-up may be appropriate; the intensity of telehealth follow-up will vary depending upon patient acuity.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: COVID-19 – Index of guideline topics".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: COVID-19 overview (The Basics)" and "Patient education: COVID-19 and pregnancy (The Basics)" and "Patient education: COVID-19 and children (The Basics)" and "Patient education: Long COVID (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Outpatient management strategies continue to evolve** – Outpatient management is appropriate for most patients with COVID-19. Management strategies continue to evolve, particularly in the setting of emerging SARS-CoV-2 variants (table 6). Clinicians should take into account the individual patient's clinical and social circumstances as well as the available resources when considering treatment options. (See 'Introduction' above and 'General principles' above.)

- **COVID-19-specific therapy**

  - **Adults who are at increased risk for severe disease due to comorbidities and/or vaccination status** – For individuals who have symptomatic mild to moderate COVID-19 (ie, no hypoxia) and are at increased risk for progression to severe disease due to advanced age, comorbidities, and/or vaccination status (table 1), we suggest early treatment with nirmatrelvir-ritonavir rather than no therapy (algorithm 1) (**Grade 2B**). These patients include:

    - Adults ≥65 years, regardless of vaccination history

    - Adults of any age with an immunocompromising condition (table 2), regardless of vaccination history or prior receipt of preexposure prophylaxis

    - Immunocompetent adults of any age who have multiple risk factors for progression to severe disease (table 1), regardless of vaccination history

    - Immunocompetent adults >50 years who have not been vaccinated, regardless of risk factors

  - Among the above, we are most likely to offer treatment to individuals with profound immunocompromise, with no history of vaccination or infection, or who are older with multiple comorbidities because these patients are at the highest risk and most likely to achieve a substantial benefit from the treatment. Other people who meet the above criteria may also benefit from treatment, but their absolute risk of hospitalization and/or death is likely small even without treatment.

- **Other adults** – For patients who do not meet the above criteria, we suggest against treatment with nirmatrelvir-ritonavir (**Grade 2C**). These individuals include immunocompetent adults aged ≤64 years who are up to date with recommended COVID-19 vaccinations (table 7) and who have one or no other risk factors for progression to severe disease (table 1). In such patients, the overall risk of progression to severe disease is so low that the absolute benefit of treatment would not outweigh any potential risk of harm (eg, medication adverse effects, drug-drug interactions, risk of "rebound COVID-19" requiring extension of the isolation period).

  We also do **not** use COVID-19-specific therapy for individuals who have asymptomatic SARS-CoV-2 infection.

- **Administration of nirmatrelvir-ritonavir** – Nirmatrelvir-ritonavir should be administered **as soon as possible** and within five days after symptom onset (algorithm 1). (See 'Nirmatrelvir-ritonavir as preferred therapy' above.)

  - **Dose** – For patients with normal renal function (estimated glomerular filtration rate [eGFR] ≥60 mL/min), the dose is nirmatrelvir 300 mg-ritonavir 100 mg orally twice daily for five days. For patients with moderate kidney impairment (eGFR 30 to 59 mL/min), the dose is nirmatrelvir 150 mg-ritonavir 100 mg orally twice daily for five days. Although the manufacturer does not recommend use in patients with severe kidney impairment, safe use with further dose reductions has been reported. (See 'Dose and administration' above.)

  - **Interactions** – Prior to prescribing nirmatrelvir-ritonavir, clinicians should review all medications and assess potential drug interactions using an online tool. Although many medications have interactions with nirmatrelvir-ritonavir, some interactions may be mitigated by holding or dose-reducing the comedication, and some interactions only warrant monitoring. Specific drug interactions can be checked through the Lexicomp Drug Interaction tool or the drug interaction checker from the University of Liverpool. (See 'Drug interactions' above.)

  - **Rebound** – Viral rebound with or without mild recurrent symptoms occurs in a minority of patients following initial improvement with nirmatrelvir-ritonavir and warrants extension of the isolation period. We advise patients of this possibility, but, for patients at risk for progression to severe disease, the potential benefits of treatment greatly outweigh any potential inconvenience from rebound. (See '"Rebound" COVID-19 after nirmatrelvir-ritonavir treatment' above.)

- **Alternative treatment options** – If nirmatrelvir-ritonavir is not available or appropriate, remdesivir is an alternative option (algorithm 1); it requires three intravenous (IV) doses over three days. (See 'Remdesivir' above.)

  Another potential alternative is high-titer convalescent plasma (limited availability). (See 'High-titer convalescent plasma' above.)

- **Outpatient therapies of limited or uncertain benefit** – Other treatments are under investigation for outpatients with nonsevere COVID-19, and evidence supporting their efficacy continues to evolve. However, high-quality data are limited and none are recommended for use outside of a clinical trial. A catalog of clinical trials can be found at covid-trials.org. (See 'Therapies of limited or uncertain benefit' above and 'Therapies that we do not recommend' above.)

In nonhospitalized patients not receiving oxygen for COVID-19, we do not treat COVID-19 with dexamethasone, prednisone, or other corticosteroids. However, patients with a concomitant acute exacerbation of asthma or chronic obstructive pulmonary disease may warrant systemic glucocorticoids as therapy for those conditions.

For patients with documented COVID-19, treatment with antibiotics, including azithromycin, is not indicated. Bacterial superinfection is not a prominent feature of COVID-19. Further, we do not routinely initiate anticoagulation or antiplatelet therapy.

- **Counseling on isolation and preventing spread of infection** — With all patients, we reinforce the importance of infection control and self-isolation and counsel them on the anticipated duration of isolation (algorithm 2). These are reviewed in detail elsewhere. (See "COVID-19: Infection prevention for persons with SARS-CoV-2 infection", section on 'Infection prevention in the home setting'.)

- **Counseling on warning symptoms** – We counsel all patients on the warning symptoms that should prompt reevaluation, including new-onset or worsening dyspnea, dizziness, and mental status changes such as confusion. (See 'Counseling on warning symptoms' above.)

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GRAPHICS

Comorbidities the CDC classifies as risk factors for severe COVID-19*[1-3]

Established, probable, and possible risk factors (comorbidities that have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review, in observational studies, or in case series):

- Age ≥65 years¶
- Asthma
- Cancer
- Cerebrovascular disease
- Children with certain underlying conditionsΔ
- Chronic kidney disease
- Chronic lung disease (interstitial lung disease, pulmonary embolism, pulmonary hypertension, bronchiectasis, COPD)
- Chronic liver disease (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)
- Cystic fibrosis
- Diabetes mellitus, type 1 and type 2
- Disabilities (eg, ADHD, cerebral palsy, congenital malformations, limitations with self-care or activities of daily living, intellectual and developmental disabilities, learning disabilities, spinal cord injuries)
- Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
- HIV
- Mental health disorders (mood disorders including depression, schizophrenia spectrum disorders)
- Neurologic conditions (dementia)
- Obesity (BMI ≥30 kg/m^2) and overweight (BMI 25 to 29 kg/m^2), or ≥95th percentile in children
- Physical inactivity
- Pregnancy or recent pregnancy
- Primary immunodeficiencies
- Smoking (current and former)
- Sickle cell disease or thalassemia
- Solid organ or blood stem cell transplantation
- Substance use disorders
- Tuberculosis
- Use of corticosteroids or other immunosuppressive medications

Possible risk factors but evidence is mixed (comorbidities have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review, but other studies had reached different conclusions):

- Alpha 1 antitrypsin deficiency
- Bronchopulmonary dysplasia
- Hepatitis B
- Hepatitis C
- Hypertension

CDC: Centers for Disease Control and Prevention; COVID-19: coronavirus disease 2019; COPD: chronic obstructive pulmonary disease; ADHD: attention deficit hyperactivity disorder; HIV: human immunodeficiency virus; BMI: body mass index.

* Listed comorbidities are associated with severe COVID-19 in all adults independent of age. People of color are also at increased risk of severe disease and death, often at a younger age, due to systemic health and social inequities.

¶ Risk of severe disease also rises steadily with age, with more than 93% of deaths occurring among adults ≥50 years and 74% of deaths occurring in adults ≥65 years.

Δ Underlying medical conditions are also associated with severe illness in children, but evidence implicating specific conditions is limited. Children with the following conditions might be at increased risk for severe illness: medical

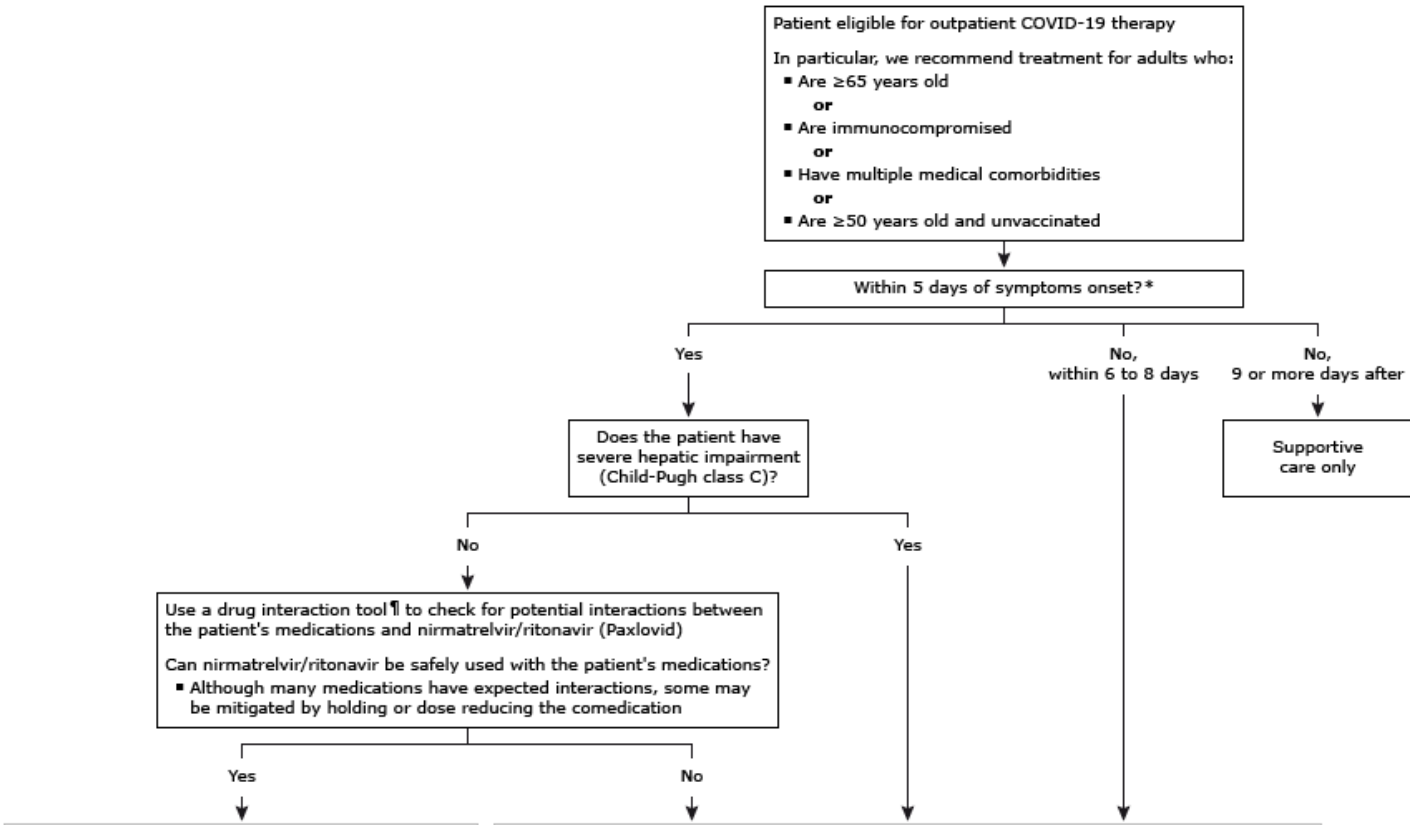
complexity; genetic, neurologic, or metabolic conditions; congenital heart disease; obesity; diabetes; asthma or other chronic lung disease; sickle cell disease; immunosuppression.

References:

1. *Centers for Disease Control and Prevention. Underlying medical conditions associated with high risk for severe COVID-19: Information for healthcare providers. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html (Accessed on March 1, 2022).*
2. *Centers for Disease Control and Prevention. Science brief: Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. Available at: https://stacks.cdc.gov/view/cdc/106171 (Accessed on August 17, 2023).*
3. *Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by age group. Available at: https://stacks.cdc.gov/view/cdc/116835 (Accessed on August 17, 2023).*

Graphic 127477 Version 16.0

Indications for and selection of COVID-19-specific therapy for adult outpatients



Administer nirmatrelvir/ritonavir (Paxlovid)
Dosing depends on renal function

eGFR	Dose
≥60 mL/min	300 mg nirmatrelvir (two 150 mg tablets) plus 100 mg ritonavir orally twice daily for 5 days
30 to 59 mL/min	150 mg nirmatrelvir plus 100 mg ritonavir orally twice daily for 5 days
<30 mL/min	Manufacturer labeling does not recommend administration, but some experts suggest use with further dose reductions[Δ]

Select among alternative options◇ (listed in order of UpToDate authors' preference)
Patients may not be eligible for all options, depending on the time since symptom onset

Agent	Time window	Dose	Clinical considerations
Remdesivir	≤7 days	200 mg IV on day 1, then 100 mg IV daily on days 2 and 3	▪ Requires parenteral administration over 3 days
Convalescent plasma	≤8 days	High-titer plasma Specific dosing is variable	▪ Requires program to collect, process, and administer ▪ Not widely available ▪ Blood typing and antibody screen required

COVID-19: coronavirus disease 2019; eGFR: estimated glomerular filtration rate; IV: intravenous; NIH: National Institutes of Health.

* The authorized time window for administration of various COVID-19-specific therapies varies by agent. We encourage treatment initiation as soon as possible after symptom onset to try to optimize efficacy.

¶ Drug interaction resources include:

- Lexicomp Interact tool
- University of Liverpool interaction tool
- US Food and Drug Administration PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers
- United States National Institutes of Health COVID-19 Treatment Guidelines

Δ Approach to alternative options vary. This algorithm reflects the approach of the contributors to the UpToDate content on management of COVID-19 in outpatients. They do not use the antiviral agent molnupiravir (Lagevrio), because the benefit is unproven and studies do not consistently demonstrate efficacy against hospitalization or death. However, the NIH COVID-19 Treatment Guidelines list molnupiravir as an alternative when nirmatrelvir/ritonavir or remdesivir are not options and do not suggest convalescent plasma as an alternative; the approach of some other UpToDate contributors is similar to the NIH guidelines.

Monoclonal antibodies are no longer recommended for treatment, because prevalent Omicron subvariants escape neutralization and render this intervention ineffective.

◇ Observational studies have described safe use of reduced doses (eg, nirmatrelvir 300 mg-ritonavir 100 mg once on day 1 followed by nirmatrelvir 150 mg-ritonavir 100 mg once daily for the next 4 days) in patients with eGFR <30 mL/min, including those on dialysis. Refer to other UpToDate content for details on potential dosing in such situations.

Graphic 139859 Version 6.0

Moderate to severe immunocompromising conditions that may result in suboptimal COVID-19 vaccine response[1]

Active treatment for solid tumor and hematologic malignancies
Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (eg, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)
Receipt of solid-organ transplant or an islet transplant and taking immunosuppressive therapy
Receipt of chimeric antigen receptor (CAR)-T cell therapy or hematopoietic cell transplant (HCT) (within 2 years of transplantation or taking immunosuppressive therapy)*
Moderate or severe primary immunodeficiency (eg, common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)
Advanced HIV infection (HIV and CD4 cell counts less than 200/microL, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV) or untreated HIV infection
Active treatment with: ▪ High-dose corticosteroids (ie, ≥20 mg prednisone or equivalent per day for ≥2 weeks) ▪ Alkylating agents ▪ Antimetabolites ▪ Transplant-related immunosuppressive drugs ▪ Cancer chemotherapeutic agents classified as severely immunosuppressive ▪ TNF blockers ▪ Other biologic agents that are immunosuppressive or immunomodulatory (eg, B cell-depleting agents)

In the United States, the Centers for Disease Control and Prevention lists the above conditions as examples of immunocompromising conditions that warrant additional COVID-19 vaccine doses. This list is not exhaustive; other immunocompromising conditions, such as impaired splenic function, may also warrant the same vaccine adjustments. Refer to other UpToDate content for specifics of vaccine doses and intervals.

CAR: chimeric antigen receptor; TNF: tumor necrosis factor; ACIP: Advisory Committee on Immunization Practices.

* For those who received COVID-19 vaccination prior to hematopoietic stem cell transplant or CAR-T cell therapy, repeat vaccination is recommended at least 3 months after the transplant or therapy.

Reference:

1. *Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (Accessed on April 24, 2023).*

Graphic 132490 Version 8.0

Prioritization for outpatient anti-SARS-CoV-2-specific therapies

Priority tier	Risk group description
1	▪ Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to underlying conditions, regardless of vaccine status (refer to immunocompromising conditions below*) **or** ▪ Unvaccinated individuals at the highest risk of severe disease (age ≥75 years or age ≥65 years with additional risk factors).
2	▪ Unvaccinated individuals at risk of severe disease not included in Tier 1 (age ≥65 years or age <65 years with clinical risk factors).
3	▪ Vaccinated individuals at risk of severe disease (age ≥65 years or age <65 with clinical risk factors). **NOTE:** Vaccinated individuals who have **not** received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment over those who have received a booster.

The NIH COVID-19 Treatment Guideline Panel prioritizes risk groups for anti-SARS-CoV-2-specific therapy based on 4 key elements: age, vaccination status, immune status, and clinical risk factors. The groups are listed by tier in descending order of priority.

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* If anti-SARS-CoV-2-specific therapy cannot be provided to all moderately to severely immunocompromised individuals, 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, including (but not limited to) patients who:

- Are receiving active treatment for solid tumor and hematologic malignancies;
- Have a hematologic malignancy (eg, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) that has been associated with poor response to COVID-19 vaccines, regardless of the patient's current treatment;
- Received a solid organ or islet transplant and are receiving immunosuppressive therapy;
- Received chimeric antigen receptor T cell (CAR T-cell) therapy or a hematopoietic cell transplant (HCT) and are within 2 years of transplantation or are receiving immunosuppressive therapy;
- Have a moderate or severe primary immunodeficiency (eg, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency disease);
- Have acquired immunodeficiency syndrome (AIDS) or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte [CD4] cell counts <200 cells/microL, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV);
- Are receiving active treatment with high-dose corticosteroids (ie, ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or immunosuppressive or immunomodulatory biologic agents (eg, B cell-depleting agents).

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

Reproduced from: COVID-19 treatment guidelines: Prioritization of anti-SARS-CoV-2 therapies for the treatment of COVID-19 in nonhospitalized patients when there are logistical constraints. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/prioritization-of-therapeutics/ (Accessed on December 8, 2022).

Graphic 134702 Version 2.0

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 15.0

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
▪ Adagrasib ▪ Atazanavir ▪ Ceritinib ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Darunavir ▪ Idelalisib ▪ Indinavir ▪ Itraconazole ▪ Ketoconazole ▪ Levoketoconazole ▪ Lonafarnib ▪ Lopinavir ▪ Mifepristone* ▪ Nefazodone ▪ Nelfinavir ▪ Nirmatrelvir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir plus dasabuvir ▪ Posaconazole ▪ Ritonavir and ritonavir-containing coformulations ▪ Saquinavir ▪ Tucatinib ▪ Voriconazole	▪ Amiodarone¶ ▪ Aprepitant ▪ Berotralstat ▪ Cimetidine¶ ▪ Conivaptan ▪ Crizotinib ▪ Cyclosporine¶ ▪ Diltiazem ▪ Duvelisib ▪ Dronedarone ▪ Erythromycin ▪ Fedratinib ▪ Fluconazole ▪ Fosamprenavir ▪ Fosaprepitant¶ ▪ Fosnetupitant-palonosetron ▪ Grapefruit juice ▪ Imatinib ▪ Isavuconazole (isavuconazonium sulfate) ▪ Lefamulin ▪ Letermovir ▪ Netupitant ▪ Nilotinib ▪ Ribociclib ▪ Schisandra ▪ Verapamil	▪ Apalutamide ▪ Carbamazepine ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Rifampin (rifampicin)	▪ Bexarotene ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone$^{\Delta}$ ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack$^{\diamond}$ ▪ Eslicarbazepine ▪ Etravirine ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pexidartinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.
- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

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* Mifepristone is a significant inhibitor of CYP3A4 when used chronically (eg, for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

¶ Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

Δ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

◇ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

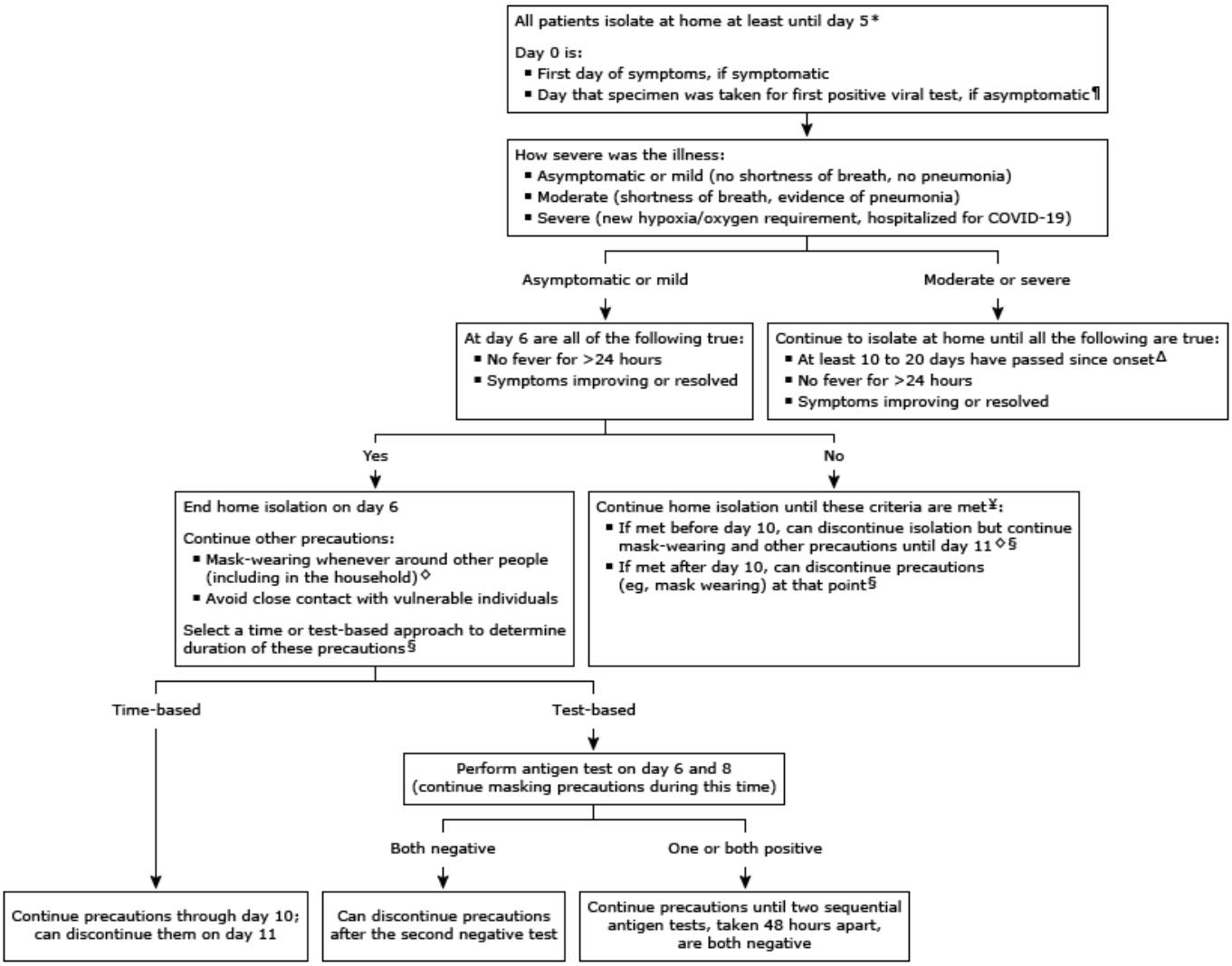
Data from: Lexicomp Online (Lexi-Interact). Copyright © 1978-2023 Lexicomp, Inc. All Rights Reserved.

References:

1. *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (January 2020) available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.*
2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

Graphic 76992 Version 95.0

Isolation and precautions for immunocompetent patients with SARS-CoV-2 infection in the community



This algorithm describes the approach to discontinuing isolation and other precautions for immunocompetent patients with SARS-CoV-2 infection in the community. This same approach should be used for persons who develop rebound infection after completing nirmatrelvir/ritonavir (Paxlovid). Refer to UpToDate content for additional information on duration of isolation/precautions, including the duration of immunocompromised persons.

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* Outpatients with suspected or confirmed SARS-CoV-2 infection (including those awaiting test results) should stay at home and try to separate themselves from other people and animals in the household. They should also avoid having visitors enter the home. Patients should wear a face mask for source control if they must be in the same room (or vehicle) as other people.

¶ If a patient was asymptomatic when they were diagnosed with SARs-CoV-2 infection, but then developed symptoms, day 0 is the first day of symptom onset.

Δ For immunocompetent patients with moderate disease, 10 days of home isolation is usually sufficient; however for those with severe disease, home isolation should generally be extended to 10 to 20. Refer to UpToDate content on infection control for persons with COVID-19 for additional information on discontinuing precautions in these populations.

◇ If a patient is unable to reliably mask around others they should continue to isolate at home for 10 days, even if they are afebrile and their symptoms are improving.

§ For most patients who are clinically improved, the need for precautions, such as masking around others, can be discontinued after 10 full days. However a test-based strategy (two negative rapid antigen tests at least 48 hours apart) may

be preferred for those who live or work with individuals at high risk for severe disease (particularly immunocompromised individuals) in settings where masks are not required (eg, non-healthcare settings).

¥ Those with ongoing fevers or no improvement in symptoms after 10 days should continue home isolation until they are fever-free for >24 hours and their symptoms have improved. Alternatively, they can discontinue isolation if they have two negative rapid antigen tests at least 48 hours apart. Such patients should also be evaluated for complications of COVID or an alternative source of their symptoms.

Graphic 139926 Version 2.0

SARS-CoV-2 Variants of Concern: Omicron sublineages[1-6]

Omicron sublineage (parent sublineage)	Therapeutic/prophylactic monoclonal antibodies			
	Tixagevimab-cilgavimab (no longer recommended)	Bebtelovimab (no longer recommended)	Sotrovimab (no longer recommended)	Casirivimab-imdevimab (no longer recommended)
BA.1	**Reduced activity**	**Active**	**Active**	Inactive
BA.2	**Active**	**Active**	Inactive	Inactive
BA.4/BA.5	**Reduced activity**	**Active**	Inactive	Inactive
BA.4.6 (BA.4)	Inactive	**Likely active**	Inactive	Inactive
BA.2.75.2 (BA.2)	Inactive*	**Likely active**	Inactive	Inactive
BQ.1/BQ.1.1 (BA.5)	Inactive	Inactive	Inactive	Inactive
XBB/XBB.1/XBB.1.5 (BA.2.10.1 and BA.2.75 recombinant)	Inactive	Inactive	Inactive	Inactive

"Variants of Concern" have evidence of an increase in transmissibility, greater risk of severe disease, a significant reduction in neutralization by antibodies generated during previous infection or vaccination, or reduced effectiveness of treatments or vaccines. Since 2022, Omicron (B.1.1.529) variants within evolving sublineages have been the predominant circulating variants globally. Prior Variants of Concern that are no longer circulating are the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants.

In the United States, the proportion of circulating variants in each state can be found on the CDC website.

Predicted activity of monoclonal antibodies against various SARS-CoV-2 variants is based on neutralizing assays that use pseudoviruses bearing the key spike protein mutations found in each variant. Neutralizing data are emerging for certain Omicron sublineages and are thus uncertain.

CDC: United States Centers for Disease Control and Prevention.

* For a related sublineage, BA.2.75, tixagevimab-cilgavimab appears to retain neutralizing activity.

References:

1. *National Institutes of Health. The COVID-19 Treatment Guidelines Panel's Statement on Omicron Subvariants and Anti-SARS-CoV-2 Monoclonal Antibodies. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-omicron-subvariants/ (Accessed on November 9, 2022).*
2. *Cao Y, Jian F, Wang J, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. BioRxiv 2022.*
3. *Takashita E, Yamayoshi S, Fukushi S, et al. Efficacy of Antiviral Agents against the Omicron Subvariant BA.2.75. New Engl J Med 2022; 387:1236.*
4. *US Food and Drug Administration. Fact sheet for healthcare providers: Emergency use authorization for bebtelovimab. Available at: https://www.fda.gov/media/156152/download (Accessed on November 9, 2022).*
5. *US Food and Drug Administration. FDA Announces Bebtelovimab is Not Currently Authorized in Any US Region. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-bebtelovimab-not-currently-authorized-any-us-region (Accessed December 1, 2022).*
6. *Imai M, Ito M, Kiso M, et al. Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB. New Engl J Med 2023; 388:89.*

Graphic 131216 Version 21.0

COVID-19 vaccines available in the United States[1-6]

Name	Platform	Indicated ages	Dose	WITHOUT moderate to severe immunocompromising condition	WITH moderate to severe immunocompromising condition	Co s ef
Moderna COVID-19 vaccine (2023-2024 Formula)	mRNA	6 months through 4 years	25 mcg (0.25 mL dark blue-capped vial)	For individuals not previously vaccinated with any COVID-19 vaccine*: ▪ Two vaccine doses 4 to 8 weeks apart¶	For individuals not previously vaccinated with any COVID-19 vaccine*: ▪ Three vaccine doses: • First two given 4 weeks apart • Third given at least 4 weeks after the second	▪ Lo in si re ▪ Sy sy (fe ch fa m he
		5 through 11 years	25 mcg dose (0.25 mL dark blue-capped vial)	For all immunocompetent individuals in these age groups: ▪ Single vaccine dose (if previously vaccinated, give at least 8 weeks after last dose)		
		12 years and older	50 mcg (0.5 mL dark blue-capped vial)			
Pfizer/BioNTech COVID-19 vaccine (2023-2024 Formula)	mRNA	6 months through 4 years[Δ]	3 mcg (0.2 mL yellow-capped vial)	For individuals not previously vaccinated with any COVID-19 vaccine*: ▪ Three vaccine doses: • First two given 3 to 8 weeks apart¶ • Third given at least 8 weeks after the second	For individuals not previously vaccinated with any COVID-19 vaccine*: ▪ Three vaccine doses: • First two given 3 weeks apart • Third given at least 8 weeks after the second	▪ Lo in si re ▪ Sy sy (fe ch fa m he
		5 through 11 years	10 mcg (0.2 mL blue-capped vial)	For all immunocompetent individuals in these age groups: ▪ Single vaccine dose (if previously vaccinated, give at least 8 weeks after last dose)	For individuals not previously vaccinated with any COVID-19 vaccine*: ▪ Three vaccine doses: • First two given 3 weeks apart • Third given at least 4 weeks after the second	
		12 years and older	30 mcg (0.3 mL gray-capped vial)			
Novavax COVID-19 vaccine (2023-2024 Formula)	Recombinant protein, adjuvanted	12 years and older	5 mcg spike protein/50 mcg adjuvant doses (0.5 mL)	For individuals not previously vaccinated with any COVID-19 vaccine: ▪ Two vaccine doses 3 to 8 weeks apart¶ For individuals who have received at least one prior COVID-19 vaccine dose (but		▪ Lo in si re ▪ Sy sy (fe ch fa

				not an updated 2023-2024 formula): ▪ Single vaccine dose at least 2 months after last dose		m h

We recommend vaccination with one of these vaccines for eligible individuals. Updated mRNA vaccines (Moderna COVID-19, 2023-2024 formula and Pfizer-BioNTech COVID-19 vaccine, 2023-2024 formula) are recommended for all vaccine doses. For individuals who cannot or will not take an mRNA vaccine, the updated Novavax COVID-19 vaccine is an alternative.

CDC: Centers for Disease Control and Prevention; COVID-19: coronavirus disease 2019.

* For individuals younger than five years of age and individuals with moderately to severely immunocompromising conditions who have already received previous vaccine doses, recommendations on updated vaccine doses depend on the number of prior vaccines received. If they have received at least three mRNA vaccine doses, the updated vaccine should be given at least eight weeks after the most recent dose. Refer to other UpToDate content for details.

¶ Although the FDA authorized intervals for the second doses of the Moderna, Novavax, and Pfizer COVID-19 bivalent vaccines are four, three, and three weeks after the first dose, respectively, the CDC suggests an interval up to eight weeks. Extending the interval to eight weeks between vaccine doses may be preferable for those (especially males aged 12 to 39 years) who have no major comorbidities and do not need to maximize protection within a shorter period of time; longer intervals may be associated with a lower risk of myocarditis and slightly improved effectiveness.[5]

Δ Children who turn five years of age during the series should receive all three doses with the formulation and dose recommended for children six months through four years.

References:

1. *SPIKEVAX (COVID-19 Vaccine, mRNA) Suspension for injection, for intramuscular use; 2023-2024 Formula. US Food and Drug Administration (FDA) approved product information. Revised September 11, 2023. Available at: https://www.fda.gov/media/155675/download?attachment (Accessed on September 11, 2023).*
2. *Fact sheet for healthcare providers administering vaccine: Emergency use authorization of Moderna COVID-19 vaccine (2023-2024 formula), for individuals 6 months through 11 years of age. Available at: https://www.fda.gov/media/167208/download?attachment (Accessed on September 11, 2023).*
3. *COMIRNATY (COVID-19 Vaccine, mRNA) suspension for injection, for intramuscular use; 2023-2024 Formula. US Food and Drug Administration (FDA) approved product information. Revised September 11, 2023. Available at: https://www.fda.gov/media/151707/download?attachment (Accessed on September 11, 2023).*
4. *Fact sheet for healthcare providers administering vaccine: Emergency use authorization of Pfizer-Biontech COVID-19 vaccine (2023-2024 formula), for 6 months through 11 years of age. Available at: https://www.fda.gov/media/167211/download?attachment (Accessed on September 11, 2023).*
5. *Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (Accessed on September 17, 2023).*
6. *US Food and Drug Administration. Emergency use authorization (EUA) of the Novavax COVID-19 vaccine, adjuvanted (2023-2024 formula), for individuals 12 years or older. Available at: https://www.fda.gov/media/159897/download (Accessed on October 4, 2023).*

Contributor Disclosures

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