COVID-19 Therapeutics for Nonhospitalized Patients—Updates and Future Directions

Antiviral therapeutics for COVID-19 in nonhospitalized patients prevent progression to severe illness, hospitalization, and death. Despite their proven benefit, utilization of these therapies remains low. This Viewpoint summarizes the therapeutic landscape in the US, discusses who is most likely to benefit from treatment, provides an update on management of COVID-19 among immunocompromised individuals, and highlights what is needed to improve COVID-19 treatment in the future.

Current Treatment Options
Randomized clinical trials conducted prior to the emergence of the Omicron variant and widespread SARS-CoV-2 vaccination demonstrated that antivirals given within 5 to 7 days of symptom onset substantially reduce risk of hospitalization and death in persons at high risk for progression to severe COVID-19. Currently, the recommended treatment options in the US for nonhospitalized patients with COVID-19 are nirmatrelvir-ritonavir (Paxlovid) and remdesivir; molnupiravir is an alternative option.1,2 All of these agents remain active against circulating Omicron subvariants. Some experts recommend use of COVID-19 convalescent plasma in immunocompromised patients, but its role is debated. Anti-SARS-CoV-2 monoclonal antibodies are no longer used because variants have evolved to become resistant to these agents.

Nirmatrelvir-ritonavir. Ritonavir-boosted nirmatrelvir is an oral SARS-CoV-2 protease inhibitor administered twice daily for 5 days. In a randomized trial conducted in unvaccinated patients at high risk for disease progression, nirmatrelvir-ritonavir reduced hospitalization or death by 86% compared with placebo. Dysgeusia and diarrhea occurred more frequently with nirmatrelvir-ritonavir than placebo. Available since early 2022 through Emergency Use Authorization (EUA), in May 2023 the US Food and Drug Administration (FDA) approved nirmatrelvir-ritonavir for the treatment of mild to moderate COVID-19 in adults at high risk for progression to severe COVID-19 and who are within 5 days of symptom onset. Pediatric use remains available only under EUA.

Because ritonavir inhibits cytochrome P3A4, nirmatrelvir-ritonavir has a number of potential drug interactions. However, these interactions can usually be managed and should not preclude use of nirmatrelvir-ritonavir in most cases. Resources to manage drug interactions include the National Institutes of Health (NIH) COVID-19 Treatment Guidelines and University of Liverpool COVID-19 Drug Interaction Checker.3 Based on extensive experience with ritonavir in pregnancy, nirmatrelvir-ritonavir may be used in pregnancy.1

Remdesivir. Remdesivir is an intravenously administered nucleotide prodrug that inhibits viral RNA polymerase. In a randomized trial that included participants who were at high risk for progression, remdesivir reduced hospitalization or death by 87% compared with placebo.3 Remdesivir is approved for adult and pediatric patients 28 days of age and older, weighing at least 3 kg, who are at high risk for progression to severe COVID-19 and within 7 days of symptom onset; the medication is administered once daily for 5 days. Clinical data for use of remdesivir in pregnancy are limited, but to date have not identified adverse effects or other concerns.

Molnupiravir. Molnupiravir inhibits viral replication by inducing viral RNA mutagenesis and is orally administered twice daily for 5 days. In a randomized trial, molnupiravir reduced hospitalization or death by 30% compared with placebo.4 This efficacy is substantially lower than that seen in the trials of nirmatrelvir-ritonavir and remdesivir. Molnupiravir is available through an EUA for treatment of adults 18 years of age and older with mild to moderate COVID-19 who are at high risk of progression to severe COVID-19 and within 5 days of symptom onset, and for whom alternative treatment options are not available or appropriate. Because animal studies raise concern for embryo-fetal and bone and cartilage toxicity, molnupiravir should not be used during pregnancy or in children. Patients should be counseled about potential risks and advised to use effective contraception during and after treatment.4

Choosing Among the Available Options
Nirmatrelvir-ritonavir is preferred for most patients because it is the only available highly effective oral antiviral. Use of nirmatrelvir-ritonavir may not be possible in some patients due to serious drug interactions, and it is not currently recommended in patients with severe kidney disease (estimated glomerular filtration rate <30 mL/min). When nirmatrelvir-ritonavir cannot be used, remdesivir is the preferred therapy, acknowledging the substantial logistical barriers and resources required to administer 3 days of intravenous treatment. If neither option is accessible or appropriate, molnupiravir may be prescribed with appropriate counseling.

Treatment of Individuals Who Have Been Vaccinated
The data demonstrating benefit of antivirals in preventing hospitalizations and deaths stem from randomized clinical trials conducted among unvaccinated, high-risk individuals, prior to Omicron variant emergence. The low hospitalization and death rates during the Omicron era and among individuals with preexisting immunity make it difficult to precisely assess the current benefit of antivirals. Nevertheless, retrospective analyses of large patient cohorts suggest that nirmatrelvir-ritonavir is...
effective among people who are vaccinated. In one study, a 73% reduction in risk of hospitalization was observed with nirmatrelvir-ritonavir compared with no treatment in 42,821 patients (2,484 treated) who were 65 years of age or older. In an analysis of 699,848 US adults who were 50 years of age or older or at least 18 years of age with an underlying health condition, nirmatrelvir-ritonavir reduced risk of hospitalization, including among vaccinated persons. Collectively, these and other studies support treatment of older patients (those >50 years and especially those ≥65 years) regardless of vaccination status, younger patients with comorbidities, and immunocompromised individuals of any age. There is likely to be a gradient of benefit with patients at greatest risk for disease progression being the most likely to benefit from treatment.

Role of Re-treatment or Extended-Duration Therapy

Symptom and/or viral rebound following nirmatrelvir-ritonavir and molnupiravir use have been reported. Although patients are often concerned about rebound, clinicians should counsel them that severe illness has not been observed and that rebound may occur even among patients who receive no therapy. It is not yet known whether a longer initial treatment course or re-treating patients is beneficial; for this reason, current guidelines do not recommend extending the duration of treatment or re-treating patients who experience symptom or viral rebound.

Treatment of Patients Who Are Immunocompromised

Initial treatment of COVID-19 for nonhospitalized patients who are immunocompromised is the same as for other patients: standard-duration nirmatrelvir-ritonavir or remdesivir, with molnupiravir as an alternative. In immunocompromised patients who have prolonged disease and evidence of persistent SARS-CoV-2 replication, some experts recommend longer courses of therapy with a preferred agent or combinations of antiviral agents. However, these recommendations are based on data from case series and other observational studies rather than randomized clinical trials. Use of convalescent plasma has also been recommended in this setting. If the use of convalescent plasma is being considered, however, it is essential to confirm that the plasma has been obtained contemporaneously and is of sufficiently high titer to neutralize the variant likely to be causing the infection.

Resistance to antiviral agents is rare but has been reported in immunocompromised individuals treated with prolonged nirmatrelvir-ritonavir and remdesivir therapy. Whether combination therapy will prevent resistance is not yet known.

Immediate Tasks and Future Directions

As the US faces increases in SARS-CoV-2 infections and hospitalizations now and in the future, clinicians and persons with acute SARS-CoV-2 infection should be aware of the importance of treatments to prevent severe COVID-19. Despite the proven effectiveness of antiviral therapy, there are concerns about rebound, clinicians should consider the need for intravenous administration (remdesivir). New drugs are clearly needed, and several are under evaluation in phase 3 clinical trials including nirmatrelvir-ritonavir and the need for intravenous administration (remdesivir). Drugs are clearly needed, and several are under evaluation in phase 3 clinical trials including nirmatrelvir-ritonavir and the need for intravenous administration (remdesivir). Drugs are clearly needed, and several are under evaluation in phase 3 clinical trials including nirmatrelvir-ritonavir and the need for intravenous administration (remdesivir). Drugs are clearly needed, and several are under evaluation in phase 3 clinical trials including nirmatrelvir-ritonavir and the need for intravenous administration (remdesivir). Drugs are clearly needed, and several are under evaluation in phase 3 clinical trials including nirmatrelvir-ritonavir and the need for intravenous administration (remdesivir). Drugs are clearly needed, and several are under evaluation in phase 3 clinical trials including nirmatrelvir-ritonavir and the need for intravenous administration (remdesivir). Drugs are clearly needed, and several are under evaluation in phase 3 clinical trials including nirmatrelvir-ritonavir and the need for intravenous administration (remdesivir).