2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Treatment and Management of COVID-19: Antiviral Treatment for Mild to Moderate COVID-19 in Adults

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ABSTRACT. This article provides a focused update to the clinical practice guideline on the treatment and management of patients with COVID-19, developed by the Infectious Diseases Society of America. The guideline panel presents nine updated recommendations on the use of nirmatrelvir/ritonavir, remdesivir, and molnupiravir, in adults with mild to moderate COVID-19. The recommendations are based on evidence derived

from a systematic literature review and adhere to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. The panel also provides a section on how to apply these recommendations, including an algorithm on the selection of antivirals.

Keywords. COVID-19; SARS-CoV-2; nirmatrelvir/ritonavir; remdesivir; molnupiravir; guideline

Posted online at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ on October 14, 2025. As COVID-19 treatment and management guidelines may change rapidly with evolving virus variants and ongoing research, please check the website for the most current version of this guideline.

In patients with mild to moderate COVID-19, does treatment with nirmatrelvir/ritonavir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Recommendation: In adults with mild to moderate COVID-19 at high risk (Table 1) or with several factors associated with increased risk for progression to severe disease (Table 2), the IDSA guideline panel recommends nirmatrelvir/ritonavir over no antiviral treatment *(strong recommendation, moderate certainty of evidence)*.

Remarks:

- Patients' medications should be screened for serious drug interactions with nirmatrelvir/ritonavir.
- Dosing based on renal function:
    - Estimated glomerular filtration rate (eGFR) >60 ml/min: 300 mg nirmatrelvir/100 mg ritonavir every 12 hours for five days
    - eGFR <60 mL/min and ≥30 mL/min: 150 mg nirmatrelvir/100 mg ritonavir every 12 hours for five days
    - eGFR <30 mL/min including hemodialysis: 300 mg nirmatrelvir/100 mg ritonavir once on day 1 and then 150 mg nirmatrelvir/100 mg ritonavir once daily on days 2-5

Recommendation: In adults with mild to moderate COVID-19 at increased but not high risk for progression to severe disease (Table 2), the IDSA guideline panel suggests using nirmatrelvir/ritonavir over no antiviral treatment *(conditional recommendation, moderate certainty of evidence)*.

Remarks:

- Patients who place a higher value on avoiding adverse events and/or drug-drug interactions and a lower value on the small reduction in hospitalization risk or faster symptom resolution may reasonably decline nirmatrelvir/ritonavir.

Recommendation: In adults without risk factors for progression to severe disease (Tables 1 and 2), the IDSA guideline panel suggests against the routine use of nirmatrelvir/ritonavir *(conditional recommendation, moderate certainty of evidence)*.

In patients with mild to moderate COVID-19, does treatment with remdesivir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Recommendation: In adults with mild to moderate COVID-19 at high risk (Table 1) or with several factors associated with increased risk for progression to severe disease (Table 2), the IDSA guideline panel recommends intravenous remdesivir over no antiviral treatment *(strong recommendation, moderate certainty of evidence)*.

Recommendation: In adults with mild to moderate COVID-19 at increased but not high risk for progression to severe disease (Table 2), the IDSA guideline panel suggests intravenous remdesivir over no antiviral treatment *(conditional recommendation, low certainty of evidence)*.

Remarks:

- Patients who place a higher value on avoiding daily intravenous infusions for 3 days and a lower value on the small reduction in hospitalization risk may reasonably decline remdesivir.

Recommendation: In adults without risk factors for progression to severe disease (Tables 1 and 2), the IDSA guideline panel suggests against the routine use of remdesivir *(conditional recommendation, moderate certainty of evidence)*.

In patients with mild to moderate COVID-19, does treatment with molnupiravir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Recommendation: In adults with mild to moderate COVID-19 at high risk (Table 1) or with several factors associated with increased risk for progression to severe disease (Table 2) *and who have no other treatment options**, the IDSA guideline panel suggests molnupiravir over no antiviral treatment *(conditional recommendation, low certainty of evidence)*.

**Other options for treatment and management of ambulatory patients include five-day treatment with oral nirmatrelvir/ritonavir or three-day treatment with intravenous remdesivir.*

Remarks:

- See Figure 1 for information from the U.S. Food and Drug Administration (FDA) Emergency Use Authorization (EUA).
- Patients who place a higher value on avoiding reproductive concerns, or the putative mutagenesis, and a lower value on the uncertain benefits would reasonably decline molnupiravir.
- Molnupiravir is not authorized under the FDA EUA for use in patients <18 years because it may affect bone and cartilage growth.
- Molnupiravir is not authorized under the FDA EUA for inpatient use.

- People who engage in sexual activity that may result in conception should use effective contraception during and for 3 months following treatment with molnupiravir. Molnupiravir is not recommended under the FDA EUA for use during pregnancy.

Recommendation: In adults with mild to moderate COVID-19 at increased but not high risk for progression to severe disease (Table 2), the IDSA guideline panel suggests against the routine use of molnupiravir *(conditional recommendation, low certainty of evidence)*.

Recommendation: In adults without risk factors for progression to severe disease (Tables 1 and 2), the IDSA guideline panel recommends against the use of molnupiravir *(strong recommendation, moderate certainty of evidence)*.

Tables 1 and 2 list examples of risk factors broadly categorized by medical condition or immunosuppressive treatment (partially adapted from Centers for Disease Control and Prevention [CDC] guidance "Underlying Conditions and the Higher Risk for Severe COVID-19") [1]. Categorization is based on cohort data from the Omicron era and may not reflect the impact on progression of increasing population immunity or variant characteristics.

The risk of progression to severe COVID-19 is a continuum influenced by various factors, including the severity of risk factor and/or immunosuppression. The categorization of risk and the examples provided in Tables 1 and 2 are illustrative and are not exhaustive or a thorough list of all conditions.

Table 1. Examples of factors associated with high risk of progression

Example health condition	Example therapeutics*
• Age ≥75 years • Fewer than 1% peripheral B-cells assessed in past 6 months • Congenital agammaglobulinemia • Graft versus host disease • Hematological malignancy on therapy • HIV infection with CD4 <200 cells/mm^3 • Other severe primary immunodeficiency • Solid organ transplant	• B-cell depleting agents in past 12 months (e.g., rituximab, ofatumumab, ocrelizumab, others) • CAR-T therapy in past 12 months • Abatacept • Tyrosine kinase inhibitor (e.g., ibrutinib, acalabrutinib, others) • High-dose corticosteroids (≥20 mg prednisone or equivalent for ≥4 weeks) • Anthracycline derivates

• Solid tumor on immunosuppressive therapy • Stem cell transplant <2 years	
*Example therapeutics that predispose to substantial immunosuppression	

Table 2. Examples of factors associated with increased but not high risk of progression*

Example health condition	Example therapeutics+
• Age 65-74 years • Atherosclerotic cardiovascular disease • Asthma • Cardiomyopathy • Cerebral vascular disease • Chronic liver diseases • Chronic lung diseases • Cirrhosis • Dementia • Diabetes Mellitus • Disabilities including Down Syndrome • End stage renal disease • Heart failure • HIV with CD4 >200 cells/mm^3 • Inflammatory bowel disease • Mental health conditions • Obesity • Parkinson's Disease • Physical inactivity • Pregnancy (current or within 6 weeks of pregnancy) • Smoking history • Solid tumor (on immunosuppressive therapy >12 months prior) • Tuberculosis	• Anti-IL-6 • Anti-IL-12 and 23 • Corticosteroids 10-20 mg for ≥4 weeks
*These factors vary in the degree of risk they confer. For those that confer less risk, the benefit of antiviral therapy will likely be lower. +Example therapeutics that are less likely to predispose to substantial immunosuppression	

Figure 1. FDA EUA criteria for the use of molnupiravir [2]

Molnupiravir may only be used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

BACKGROUND AND APPROACH TO RISK CATEGORIZATION

Mild to moderate COVID-19 is defined as symptoms of respiratory infection with oxygen saturation >94% on room air without the need for supplemental oxygen (Figure 2). Over the past few years, and particularly since December 2021, the risk of severe COVID-19, hospitalization, and death have substantially decreased because of increased immunity and the emergence of the Omicron variant. Therefore, the panel decided to adopt a risk-based approach to recommending antiviral treatment recognizing that the strength of recommendation will likely be sensitive to varying baseline risks.

Figure 2. Stages of COVID-19 Severity (Positive antigen or molecular test for SARS CoV-2)

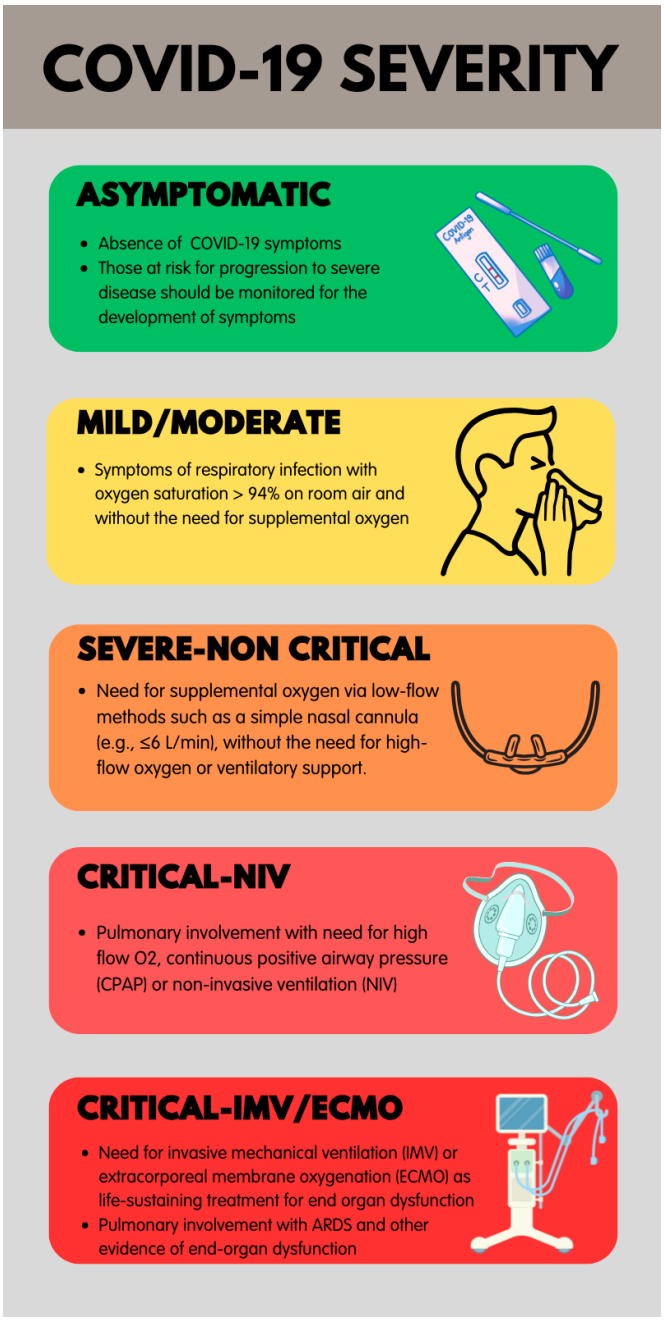


Figure adapted from Shumaker AH, Bhimraj A. Pharmacologic treatment and management of coronavirus disease 2019. Infect Dis Clin North Am 2022; 36(2):349-64.

As mortality risk among patients hospitalized primarily for COVID-19 has substantially decreased [3], avoiding morbidity leading to hospitalization was the major driver for recommendations on the use of antiviral agents. The CDC reported that cumulative COVID-19-related hospitalization rates dropped in all age groups but remained significantly elevated in those aged 65 years and older [4].

The guideline panel set a threshold for a minimum clinically meaningful reduction of hospitalizations for any antiviral treatment at 10 to 20 in 1,000 (i.e., an expected 1-2% fewer hospitalizations from baseline).

To estimate the risk for hospitalization in patients with risk factors for progression to severe disease, the panel relied on event rates from the untreated control arms of recent randomized controlled trials (RCTs) because obtaining homogenous risk groups is challenging. For example, the PANORAMIC trial [5] started enrollment in December 2021 at the beginning of the Omicron period and appeared to provide a reasonable estimate of hospitalization risk in the placebo group. Despite a substantial proportion of participants in the PANORAMIC trial having risk factors for progression to severe outcomes, only 96 of 12,525 (0.77%) patients with COVID-19 required hospitalization. Based on progression rates in PANORAMIC, the panel judged that the group without risk factors for progression to severe disease would have an expected hospitalization rate of 0.5% (or even substantially lower).

In contrast, numerous medical conditions and immunosuppressive drugs increase the risk for progression to severe disease, of which B-cell depleting agents and hematologic malignancies are high on the list. It is important to note that the risk of progression to severe COVID-19 is a continuum influenced by various factors, including the degree of immunosuppression. Based on progression rates in cohort studies [6,7], the panel judged that those at high risk or with several factors associated with increased risk for progression to severe disease would have an expected hospitalization rate of at least 6%. For example, the risk of hospitalization has been reported as high as 20-50% range among cancer patients [7], though selection bias is difficult to completely exclude.

The panel then judged that those with increased but not high risk for progression to severe disease would have an expected hospitalization rate of >0.5 to <6%; the panel used the midpoint of this range (3%) for illustrative purposes in the Evidence Profiles. This category is a heterogeneous group, with substantial uncertainty regarding risk for progression. Observational studies are often discordant regarding risk of progression for a particular population (e.g., patients with chronic liver diseases, or those living with mental health conditions) [8]. The group was selected to accommodate conditions and therapeutics which historically have been thought to elevate risk for adverse COVID-19 outcomes but are now considered less likely to cause significant immunosuppression (e.g., use of tumor necrosis factor-alpha inhibitors) [9].

Rationale for Using Anti–SARS-CoV-2 Antivirals

Three direct-acting antivirals are currently available to target SARS-CoV-2 replication at different enzymatic steps:

• **Nirmatrelvir/ritonavir (Paxlovid)** blocks the viral main protease (Mpro), halting polyprotein cleavage and replication. Ritonavir boosts nirmatrelvir levels via CYP3A4 inhibition, allowing twice-daily oral dosing. The agent carries full FDA approval for adults with mild-to-moderate COVID-19 who are at high risk for progression to severe disease and remains under Emergency Use Authorization (EUA) for adolescents ≥12 years (weight ≥40 kg) [10,11].

• **Remdesivir (Veklury)** is a nucleotide analogue that binds the viral RNA-dependent RNA polymerase, causing premature chain termination of viral RNA. Initially reserved for in-hospital use, it now has full FDA approval for both hospitalized patients and high-risk outpatients (three-day IV course) across all age groups—from term neonates (≥1.5 kg) through adults [12,13].

• **Molnupiravir (Lagevrio)** is an oral pro-drug converted to β-D-N4-hydroxycytidine (NHC), then phosphorylated to the active triphosphate (NHC-TP) before incorporation into viral RNA by the viral RNA polymerase, inducing lethal mutagenesis. It is available through an EUA for adults ≥18 years with mild to moderate COVID-19 who are at high risk for severe outcomes [14].

Most people with mild to moderate COVID-19 cases are managed as outpatients, though some are encountered in emergency or inpatient settings; treatment decisions depend on disease severity, not venue, so the guideline addresses anti-SARS-CoV-2 antivirals by severity rather than setting.

METHODS

The panel's recommendations are based on evidence derived from systematic reviews and adhere to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (Supplementary Figure 1) [15]. The recommendations have been endorsed by the Society of Critical Care Medicine and the Society for Healthcare Epidemiology of America.

Strong recommendations ("the panel recommends") are made when the recommended course of action would apply to most people with few exceptions. Conditional recommendations ("the panel suggests") are made when the suggested course of action would apply to the majority of people with many exceptions and shared decision making is important.

Literature searches were conducted in September 2024 as part of the systematic reviews. Key eligibility criteria at both the topic and clinical question levels guided the selection of studies for inclusion.

A critical appraisal of the evidence according to the GRADE approach, along with an assessment of the benefits and harms of care options informed the recommendation(s) [15,16]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

NIRMATRELVIR/RITONAVIR

SUMMARY OF EVIDENCE FOR NIRMATRELVIR/RITONAVIR

The literature search identified four RCTs reporting on treatment of mild to moderate COVID-19 in patients at risk for progression to severe disease with nirmatrelvir/ritonavir [11,17-20] in ambulatory and hospital settings (Supplementary Table 1). These studies reported on the following outcomes: mortality, hospitalization, serious adverse events, adverse events requiring discontinuation of treatment, and symptom resolution (Table 3).

Table 3. GRADE Evidence Profile: In patients with mild to moderate COVID-19, does treatment with nirmatrelvir/ritonavir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirmatrelvir / ritonavir	No nirmatrelvir / ritonavir*	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 28 days)												
4[11,17-19]	randomized trials	not serious	not serious	not serious	very serious[a]	none	18/1893 (1.0%)	0.1%	**RR 0.53** (0.18 to 1.58)	**0 fewer per 1,000** (from 1 fewer to 1 more)	⊕⊕◯◯ Low	CRITICAL
								0.5%		**2 fewer per 1,000** (from 4 fewer to 3 more)		
								3.0%		**14 fewer per 1,000** (from 25 fewer to 17 more)		
Hospitalization (follow-up: 28 days)												
2[11,18]	randomized trials	not serious	not serious	not serious[b]	serious[a]	none	13/1693 (0.8%)	0.5%	**RR 0.17** (0.10 to 0.31)	**4 fewer per 1,000** (from 5 fewer to 3 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
								3.0%		**25 fewer per 1,000** (from 27 fewer to 21 fewer)		
								6.0%		**50 fewer per 1,000** (from 54 fewer to 41 fewer)		
Serious adverse events												
3[11,17,18]	randomized trials	not serious	not serious	not serious	serious[a]	none	32/1895 (1.7%)	91/1881 (4.8%)	**RR 0.52** (0.20 to 1.35)	**23 fewer per 1,000** (from 39 fewer to 17 more)	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirmatrelvir / ritonavir	No nirmatrelvir / ritonavir*	Relative (95% CI)	Absolute (95% CI)		
Adverse events requiring discontinuation of treatment												
3[11,17,18]	randomized trials	not serious	not serious	not serious	serious[a]	none	24/1895 (1.3%)	9/1881 (0.5%)	**RR 0.75** (0.5 to 1.13)	**26 fewer per 1,000** (from 53 fewer to 14 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Symptom resolution for patients at high risk (follow-up: 28 days)[c]												
1[20]	randomized trials	not serious	not serious	not serious	serious[d]	none	619/970 (63.8%)	566/986 (57.4%)	**HR 1.20** (1.07 to 1.35)	**67 more per 1,000** (from 25 more to 110 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Symptom resolution for all patients (follow-up: 28 days)[e]												
2[18,20]	randomized trials	not serious	not serious	not serious	serious[f]	none	1066/1624 (65.6%)	1036/1620 (64.0%)	**RR 1.02** (0.97 to 1.08)	**13 more per 1,000** (from 19 fewer to 51 more)	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

*For mortality and hospitalization, percentages represent illustrative baseline risks for patients without risk factors for progression to severe disease, patients at increased but not high risk, and patients at high risk.

Explanations

a. Few events do not meet the optimal information size and suggest fragility in the estimate.

b. Study data from pre-Omicron era; hospitalization rates have significantly declined potentially affecting the effect estimate resulting in indirectness. Baseline risk indirectness was judged to be less indirect for the lowest and highest risk category, so the panel decide to not rate down the certainty of evidence.

c. Median time to resolution: NMV/r 16 days (95% CI: 15, 18) vs. placebo 19 days (95% CI: 18, 20)

d. 95% CI crossing threshold of meaningful difference; median time to resolution: 95% CI not completely separated

e. Median time to resolution: NMV/r 16 days (95% CI: 15, 18) vs. placebo 19 days (95% CI: 18, 20) for EPIC-HR; 12 days (95% CI: 11, 13) vs. 13 (95% CI: 12, 14) in EPIC-SR

f. 95% CI includes no effect as well as small effect

BENEFITS OF NIRMATRELVIR/RITONAVIR

Though the evidence for prevention of hospital admission by antiviral therapy drove the panel's recommendations, mortality data from all care settings are also presented to illustrate the downstream effects of antiviral treatment.

Two RCTs showed a relative risk reduction in hospitalizations of 83% (Supplementary Figure 3). For the high-risk patient group, this translates into a robust absolute risk reduction of 50 fewer hospitalizations per 1,000 (95% CI: 54 fewer to 41 fewer) exceeding the threshold set by the panel of at least 20 hospitalizations in 1,000 (moderate certainty of evidence). In contrast, for patients without risk factors, only 4 fewer hospitalizations in 1,000 (95% CI: 4 fewer to 1 fewer) would be expected, limiting the usefulness of antiviral treatment in this population.

The use of nirmatrelvir/ritonavir in high-risk patients may also lead to faster symptom resolution (HR 1.2, 95% CI 1.07, 1.35) [20].

All-cause mortality through day 28 pooled from 4 trials may be lower in patients receiving nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir (RR: 0.53; 95% CI: 0.18, 1.58, low certainty of evidence; Supplementary Figure 2). The certainty of evidence was rated down due to few events leading to an imprecise estimate.

HARMS OF NIRMATRELVIR/RITONAVIR

Evidence from RCTs in patients with mild to moderate COVID-19 receiving nirmatrelvir/ritonavir demonstrate fewer serious adverse events (SAEs) (RR 0.52, 95% CI: 0.20, 1.35; Supplementary Figure 4), suggesting that most SAEs are related to the underlying illness rather than the antiviral treatment, as well as fewer adverse events (RR 0.75, 95% CI: 0.50, 1.13, Supplementary Figure 5). There was a higher rate of dysgeusia in the nirmatrelvir/ritonavir group compared to placebo, 5.8% vs. 0.2%, respectively [18].

Co-administration is contraindicated with agents whose concentrations are markedly altered by nirmatrelvir/ritonavir or with agents that accelerate its metabolism. These interactions can undermine antiviral efficacy and promote resistance, leading to treatment failure. They can also cause serious

adverse events or life-threatening toxicity from elevated levels of concomitant medications (Figures 3 and 4).

Figure 3. Drugs that are primarily metabolized by CYP3A for which elevated concentrations are associated with serious and/or life-threatening reactions* [21]

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine (in patients with renal and/or hepatic impairment)
- Antipsychotics: lurasidone, pimozide
- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: such as lovastatin, simvastatin (these drugs can be temporarily discontinued to allow nirmatrelvir/ritonavir use)
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- Vasopressin receptor antagonists: tolvaptan

*Please check drug interactions before initiating nirmatrelvir/ritonavir as not list all therapeutic agents or classes with potential interactions are listed; see **Liverpool COVID-19 interactions website**.

Figure 4. Drugs that are strong CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer [21]

- Anticancer drugs: apalutamide, enzalutamide
  - Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
  - Antimycobacterials: rifampin, rifapentine
  - Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
  - Herbal products: St. John's Wort (*hypericum perforatum*)

Less severe but clinically meaningful drug interactions may also occur when nirmatrelvir/ritonavir is co-administered with other agents. Levels of immunosuppressive agents such as tacrolimus, cyclosporine, or sirolimus can be increased when administered with nirmatrelvir/ritonavir. Although dose adjustments are possible, the narrow therapeutic index, risk of toxicity, and challenges in managing these interactions may make concomitant use inadvisable in many settings. Hormonal contraceptives containing ethinyl estradiol may have reduced effectiveness due to lowered ethinyl estradiol levels when administered with nirmatrelvir/ritonavir. Women of childbearing potential should be counseled to use a back-up, non-hormonal method of contraception for one menstrual cycle after stopping nirmatrelvir/ritonavir. Although nirmatrelvir/ritonavir has numerous potential drug-drug interactions, most can be effectively managed through temporary discontinuation, dose adjustment, or substitution of the interacting medication. Therefore, providers should not routinely avoid its use solely due to interaction concerns.

OTHER CONSIDERATIONS FOR NIRMATRELVIR/RITONAVIR

The panel agreed that the overall certainty of the evidence for the treatment of patients was moderate due to concerns about imprecision (Supplementary Table 2). The panel agreed that the benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk of severe disease; however, recognized concerns with drug interactions must be considered.

The evidence confirms that using nirmatrelvir/ritonavir early in the disease process confers maximum benefit. It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course. Observational studies have shown a similar benefit among vaccinated patients infected with newer variants [22,23].

Symptomatic viral rebound in patients treated with and without antiviral agents, including nirmatrelvir/ritonavir

Symptomatic viral rebound has been estimated to occur in 0.8% to 6.6% of nirmatrelvir/ritonavir-treated patients in various trials, including EPIC-HR (Table 4) [24-27]. Symptom recurrence has also been described with molnupiravir (5.9%) [26] and no antiviral treatment [24,29]. Symptom recurrence has generally not been associated with hospitalization [30,31]. No comparative evidence was found on the effect of repeat treatment with nirmatrelvir/ritonavir (on any other direct-acting antivirals) in patients experiencing symptomatic viral rebound after initial antiviral treatment. The effectiveness of repeating the same antiviral in this context remains unknown, particularly with respect to patient-important outcomes such as hospitalization, need for invasive ventilation, or death. Study limitations of observational medical records database studies include misclassifications in admission diagnosis and absence of adequate compliance determination, among others.

Table 4. GRADE Evidence Profile: In patients with mild to moderate COVID-19 at high risk for progression to severe disease, does treatment with nirmatrelvir/ritonavir vs. no treatment affect symptom recurrence or viral rebound after completion of course of nirmatrelvir/ritonavir?

Certainty assessment							Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Hospitalizations or all-cause deaths									
5[24-28]	observational studies[a]	serious[b]	not serious	not serious	not serious	none	• No direct evidence was found investigating the effect of repeat nirmatrelvir/r (n/r) treatment in patients experiencing symptomatic viral rebound after initial antiviral treatment. • Rates of viral rebound after n/r treatment have been estimated to be in the range of 2.3% (23/990) in the registration trial EPIC-HR to 3.5% (398/11,270; Wang 2022) and seen in Wong 2023 at 6.6% (16/242). • Comparative rates of viral rebound have been seen in untreated persons in the registration trial EPIC-HR (17/980; 1.7%) and in Wong 2023 (170/3787; 4.5%). • Molnupiravir rebound has been reported to occur in 5.9% (139/2374; Wang 2022) and seen in data from Wong 2023 (27/563; 4.8%) • Observational evidence showed hospitalization after n/r has been infrequent, ranging from 0.11% (6/5,287) to 0.4% (2/483) and 0.44% (50/11,270) for n/r; and 0.84% for molnupiravir [25,28] • 2 deaths out of 6 patients occurred in those hospitalized in one study. • The effect of repeating the same drug (for another course) after a viral rebound is unknown for patient important outcomes. • Study limitations of observational medical records database studies include misclassifications in admission diagnosis and absence of adequate compliance determination, among others.	⊕◯◯◯ Very Low*	CRITICAL
Serious adverse events - not reported									
-	-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

*Certainty ratings derived from evidence that has not been peer reviewed or published.

CI: confidence interval; **RR:** risk ratio

Explanations

a. Rates derived from arms of RCTs are observational in nature (and indirect as it relates to the clinical question) as no comparative effectiveness of repeat treatment in viral rebound was found.
b. No comparative effectiveness available.

CONCLUSIONS AND RESEARCH NEEDS FOR NIRMATRELVIR/RITONAVIR

The guideline panel recommends the use of nirmatrelvir/ritonavir for patients with mild to moderate COVID-19 at high risk for progression to severe disease who are within five days of symptom onset. However, patients with mild to moderate COVID-19 without risk factors (and an estimated hospitalization risk of 0.5% or less) are unlikely to benefit from antiviral treatment. Patients with increased but not high risk may or may not benefit from antiviral treatment, and treatment is only suggested after applying shared decision making weighing the benefits and potential downsides of treatment.

REMDESIVIR

SUMMARY OF EVIDENCE FOR REMDESIVIR

The literature search identified five RCTs (Supplementary Table 1) assessing the outcomes of mortality, hospitalizations for any cause, and COVID-19-related medically attended visits, as well as serious adverse events (Table 5) [13,32-35]. One RCT compared treatment with three days of intravenous (IV) remdesivir (200 mg on day one followed by 100 mg on days two and three) initiated within 7 days of symptom onset to no treatment with remdesivir in unvaccinated patients [13]. The study enrolled patients at high risk for progression (e.g., with obesity, diabetes mellitus, hypertension, immune compromise) or age 60 years or older without prior treatment (e.g., monoclonal antibodies) who were not expected to receive oxygen at time of enrollment (>94% on room air).

Table 5. GRADE Evidence Profile: In patients with mild to moderate COVID-19, does treatment with remdesivir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Remdesivir**	**No remdesivir***	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow-up: 28 days)												
5[13,32-35]	randomized trials	not serious	not serious	not serious	serious[a]	none	56/1545 (3.6%)	0.1%	**RR 0.83** (0.57 to 1.19)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
								0.5%		**1 fewer per 1,000** (from 2 fewer to 1 more)		
								3.0%		**5 fewer per 1,000** (from 13 fewer to 6 more)		
Hospitalization (all-cause) (follow-up: 28 days)												
1[13]	randomized trials	not serious	not serious	not serious[b]	serious[c]	none	5/279 (1.8%)	0.5%	**HR 0.28** (0.10 to 0.75)	**4 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
					very serious[c]			3.0%		**22 fewer per 1,000** (from 27 fewer to 7 fewer)	⨁⨁◯◯ Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	No remdesivir*	Relative (95% CI)	Absolute (95% CI)		
					serious[c]			6.0%		**43 fewer per 1,000** (from 54 fewer to 15 fewer)	⊕⊕⊕◯ Moderate	
Covid-19-related medically attended visits (follow-up: 28 days)												
1[13]	randomized trials	not serious	not serious	not serious	serious[c]	none	4/246 (1.6%)	21/252 (8.3%)	**HR 0.19** (0.07 to 0.56)	**67 fewer per 1,000** (from 77 fewer to 36 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT
Symptom alleviation												
1[13]	randomized trials	not serious	not serious	not serious	serious[c]	none	23/66 (34.8%)	15/60 (25.0%)	**RR 1.60** (0.74 to 3.48)	**150 more per 1,000** (from 65 fewer to 620 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Serious adverse events												
4[13,32-34]	randomized trials	not serious	not serious	not serious	serious[c]	none	98/688 (14.2%)	77/612 (12.6%)	**RR 0.78** (0.61 to 1.00)	**28 fewer per 1,000** (from 49 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

*For mortality and hospitalization, percentages represent illustrative baseline risks for patients without risk factors for progression to severe disease, patients at increased but not high risk, and patients at high risk.

Explanations

a. 95% CI includes the potential for appreciable benefit but cannot exclude the potential for harm.

b. Study data from pre-Omicron era; hospitalization rates have significantly declined potentially affecting the effect estimate resulting in indirectness. Baseline risk indirectness was judged to be less indirect for the lowest and highest risk category and therefore the panel decide to not rate down the certainty of evidence.

c. Few events do not meet the optimal information size and suggest fragility in the estimate. For the outcome of hospitalization: at baseline risks of 0.5%, the entire 95% CI of the absolute risk difference is within the no effect boundary and only fragility is present (rated down once); at baseline risk of 3%, the 95% CI of the absolute risk difference includes appreciable benefits as well little or no effect on hospitalization: rated down twice; at 6% baseline risk, the entire 95% CI of the absolute risk reduction is above the panel determination of minimally important difference (rated down once).

BENEFITS OF REMDESIVIR

Treatment with remdesivir for three days in ambulatory patients reduced hospitalizations and COVID-19-related medically attended visits through day 28 (HR: 0.28; 95% CI: 0.1, 0.75, low to moderate certainty of evidence, depending on baseline risk; and HR: 0.19; 95% CI: 0.07, 0.56, moderate certainty of evidence, respectively). For the high-risk patient group, this translates into 45 fewer hospitalizations per 1,000 (95% CI: 54 fewer to 15 fewer) exceeding the threshold set by the panel of at least 20 hospitalizations in 1,000 (moderate certainty of evidence). In contrast, for patients without risk factors, only 4 fewer hospitalizations in 1,000 (95% CI: 4 fewer to 1 fewer) would be expected, limiting the usefulness of antiviral treatment in this population. COVID-19 related mortality may be lower in patients receiving remdesivir rather than placebo (RR 0.83; 95% CI: 0.57, 1.19, moderate certainty of evidence; Supplementary Figure 6); however, given the small baseline risk of mortality, the reduction may not be clinically meaningful (absolute effect: up to 5 fewer per 1,000 persons in the highest risk group; 95% CI: from 13 fewer to 6 more). In the PINETREE RCT, no deaths were observed in the treatment or control arms [13].

HARMS OF REMDESIVIR

Remdesivir infusions did not appear to be associated with a greater risk of serious adverse events compared to no remdesivir (RR: 0.78; 95% CI: 0.61, 1.00, moderate certainty of evidence; Supplementary Figure 7).

OTHER CONSIDERATIONS FOR REMDESIVIR

The panel agreed that the overall certainty of evidence for the treatment of patients with mild to moderate COVID-19 was low to moderate (depending on baseline risk; Table 5) due to concerns about imprecision, as less than half of the original projected sample size was enrolled leading to few events and fragility of the effect estimate [13] (Supplementary Table 2). However, compared to prior trials, giving remdesivir early in the course of the viral infection appears to have a robust effect within the limitation of a limited sample size. The panel agreed that benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk for severe disease. The evidence confirms that using remdesivir early in the

disease process confers maximum benefit. It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course.

While effective, remdesivir is administered intravenously, which may present logistical challenges in the outpatient setting. These include the need for three consecutive days of IV access, potential complications related to IV placement, and higher costs compared to oral antiviral agents. These practical considerations, along with patient preferences and access to infusion facilities, should be part of a shared decision-making process between the provider and patient.

No dosage adjustment is needed for remdesivir for any degree of renal dysfunction, including hemodialysis.

CONCLUSIONS AND RESEARCH NEEDS FOR REMDESIVIR

The guideline panel recommends remdesivir for patients with mild to moderate disease who are at high risk for severe COVID-19. However, patients with mild to moderate COVID-19 without risk factors (and an estimated hospitalization risk of 0.5% or less) are unlikely to benefit from antiviral treatment. Patients with increased but not high risk may or may not benefit from antiviral treatment, and treatment with remdesivir is only suggested after applying shared decision making weighing the benefits and potential downsides of treatment.

MOLNUPIRAVIR

SUMMARY OF EVIDENCE FOR MOLNUPIRAVIR

Ten RCTs informed the recommendation for molnupiravir (Supplementary Table 1) [5,14,19,36-42]. The RCTs reported on the effect of treating at least partially vaccinated participants with COVID-19 with either 800 mg of molnupiravir or placebo, evaluating the outcomes of mortality, hospitalization, symptom improvement, and adverse and serious adverse events (Table 6). In the largest trial (n=26,411), PANORAMIC, 99% of participants had at least one COVID-19 vaccine dose with 92-93% having received three doses [5]. Two RCTs reported on treatment of unvaccinated patients with COVID-19 with either 800 mg of molnupiravir or placebo for five days [38,39]. In one phase III trial (MOVe-OUT trial) reporting on the outcomes of death,

hospitalization and serious adverse events, patients with mild to moderate COVID-19 received either molnupiravir or placebo within five days after the onset of symptoms. A phase IIa trial reported on the outcomes of death and serious adverse events in patients with symptom duration <7 days who received molnupiravir or placebo [38].

Table 6. GRADE Evidence Profile: In patients with mild to moderate COVID-19, does treatment with molnupiravir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Molnupiravir	No molnupiravir*	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 28 days to 29 days)												
8[5,19,36-41]	randomized trials	not serious	not serious	not serious	serious[a]	none	82/14818 (0.6%)	0.1%	**RR 0.89** (0.68 to 1.17)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
								0.5%		**1 fewer per 1,000** (from 2 fewer to 1 more)		
								3.0%		**3 fewer per 1,000** (from 10 fewer to 5 more)		
Hospitalizations (follow-up: 29 days)												
6[5,37-41]	randomized trials	serious[b]	not serious	not serious[c]	not serious[a]	none	169/14301 (1.2%)	0.5%	**RR 0.86** (0.70 to 1.05)	**1 fewer per 1,000** (from 2 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
					serious[a]			3.0%		**4 fewer per 1,000** (from 9 fewer to 2 more)	⊕⊕◯◯ Low	
					serious[a]			6.0%		**8 fewer per 1,000** (from 18 fewer to 3 more)	⊕⊕◯◯ Low	
Fatigue improvement/resolution, sustained (failures) (follow-up: 29 days)[d]												
1[14]	randomized trials	not serious	not serious	not serious	not serious[e]	none	64/538 (11.9%)	86/528 (16.3%)	**RR 0.73** (0.54 to 0.99)	**44 fewer per 1,000** (from 75 fewer to 2 fewer)	⊕⊕⊕◯ Moderate[a]	IMPORTANT
Cough improvement/resolution, sustained (failures) (follow-up: 29 days)[f]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Molnupiravir	No molnupiravir*	Relative (95% CI)	Absolute (95% CI)		
1[14]	randomized trials	not serious	not serious	not serious	serious[e]	none	78/570 (13.7%)	91/574 (15.9%)	**RR 0.86** (0.65 to 1.14)	**22 fewer per 1,000** (from 55 fewer to 22 more)	⨁⨁⨁◯ Moderate[a]	IMPORTANT
Serious adverse events (follow-up: range 28 days to 29 days)												
9[5,19,36-42]	randomized trials	not serious	not serious	not serious	not serious	none	100/15287 (0.7%)	83/15064 (0.6%)	**RR 0.78** (0.49 to 1.24)	**1 fewer per 1,000** (from 3 fewer to 1 more)	⨁⨁⨁⨁ High	CRITICAL
Adverse events												
9[5,19,36-42]	randomized trials	not serious	not serious	not serious	not serious	none	320/15202 (2.1%)	196/15064 (1.3%)	**RR 0.95** (0.78 to 1.17)	**1 fewer per 1,000** (from 3 fewer to 2 more)	⨁⨁⨁⨁ High	IMPORTANT

CI: confidence interval; **RR:** risk ratio

*For mortality and hospitalization, percentages represent illustrative baseline risks for patients without risk factors for progression to severe disease, patients at increased but not high risk, and patients at high risk.

Explanations

a. 95% CI of the absolute risk reduction does not include any appreciable benefit or harm for the lowest baseline risk: not rated down. For the higher baseline risk population, some appreciable benefits may be included in the 95% CI of the absolute risk reduction, particularly in the high group, making the estimate less precise: rated down once.

b. As Butler 2023 was open label, close to 90% of enrolled patients in the pooled estimate was unblinded leading to potential differential management.

c. Some study data from pre-omicron era; hospitalization rates have significantly declined potentially affecting the effect estimate resulting in indirectness. Baseline risk indirectness was judged to be less indirect for the lowest and highest risk category and therefore the panel decide to not rate down the certainty of evidence.

d. Median time to resolution: 6 days for molnupiravir (95% CI 6 to 7); 7 days for placebo (95% CI: 6 to 8); HR: 1.15 (1.01, 1.31)

e. 95% CI includes appreciable benefit as well as no clinically relevant benefit

f. Median time to resolution: 10 days for molnupiravir (95% CI 9 to 11); 10 days for placebo (95% CI: 8 to 11); HR: 1.04 (0.92, 1.18)

BENEFITS OF MOLNUPIRAVIR

Molnupiravir may prevent COVID-19 related hospitalizations, but the pooled relative effect estimate was imprecise (RR: 0.86; 95% CI: 0.70, 1.05, moderate to low certainty of evidence depending on assumed baseline risk; Supplementary Figure 8).

For the high-risk patient group, this translates into 8 fewer hospitalizations per 1,000 (95% CI: 18 fewer to 3 more; low certainty of evidence).

COVID-19-related mortality may be lower in patients receiving molnupiravir rather than placebo (RR: 0.89; 95% CI: 0.68, 1.17, moderate certainty of evidence; Supplementary Figure 9); however, given the small baseline risk of mortality across the available evidence, the reduction in mortality may not be clinically meaningful (absolute effect: up to 3 fewer per 1,000 persons in the highest risk group; 95% CI: from 10 fewer to 5 more).

One adequately blinded RCT reported on improvement of COVID-19 symptoms [14]. Fatigue and cough improved more frequently than with placebo (RR for fatigue: 0.73; 95% CI 0.54, 0.99; moderate certainty of evidence; and RR for cough: 0.86; 95% CI 0.65, 1.14; moderate certainty of evidence).

HARMS OF MOLNUPIRAVIR

Patients treated with molnupiravir may not experience greater serious adverse events or adverse events than those receiving placebo (RR for serious adverse events: 0.78; 95% CI: 0.49, 1.24, high certainty of evidence; Supplementary Figure 10; and RR for adverse events: 0.95; 95% CI: 0.78, 1.17, high certainty of evidence; Supplementary Figure 11).

Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered during pregnancy [2]. Molnupiravir raises particular concerns in immunocompromised individuals, who may have prolonged viral shedding and impaired clearance, increasing the theoretical risk of treatment-associated viral mutagenesis. Females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for four days after the last dose. Breastfeeding is not recommended during treatment with molnupiravir. Lactating individuals may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for four days after

last dose of molnupiravir [43]. Men of reproductive potential who are sexually active with females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for at least three months after the last dose of molnupiravir. It is also not recommended in children <18 years of age for the concern of bone growth.

Molnupiravir does not require renal or hepatic dose adjustment.

OTHER CONSIDERATIONS FOR MOLNUPIRAVIR

The panel agreed that the overall certainty of evidence for treatment of patients with mild to moderate COVID-19 was low in favor of molnupiravir treatment in the higher risk groups (given concerns with imprecision, and a relatively small effect), and moderate for the absence of clinically relevant effect in patients without risks for progression to severe disease (Supplementary Table 2).

Molnupiravir use presents additional considerations and potential concerns regarding viral mutagenesis in immunocompromised persons and safety in persons of reproductive age, for which more data are needed to quantify such effects. The panel recognizes that alternative treatment options exist with the possibility of greater benefit and fewer safety concerns. The FDA required manufacturers to conduct additional animal studies on the impact of the drug on spermatogenesis and to establish a pregnancy registry if the drug was inadvertently administered during pregnancy [44]. At the time of publication, there are no published pregnancy cases in the registry.

CONCLUSIONS AND RESEARCH NEEDS FOR MOLNUPIRAVIR

The guideline panel suggests the use of molnupiravir for patients with mild to moderate COVID-19 at high risk for progression to severe disease who are within five days of symptom onset and have no other treatment options, particularly for patients at highest risk such as treatment with B-cell depleting agents. However, patients with mild to moderate COVID-19 without risk factors (and an estimated hospitalization risk of 0.5% or less) are unlikely to benefit from antiviral treatment and the guideline panel recommends against using molnupiravir in this situation. Patients with increased risk (but not at high risk) may not benefit from

antiviral treatment, and the guideline panel suggests against routine treatment with molnupiravir while applying shared decision making weighing the benefits and potential downsides of treatment.

More data are needed on the potential adverse effects of this medication.

How to apply guidelines to management of ambulatory patients with mild to moderate COVID-19

Patients presenting with COVID-19 should be assessed for disease severity prior to any clinical decision making regarding therapeutic options (Figure 2). Identifying the patient's disease severity is necessary to ensure that the agents are used in the way they were studied for COVID-19 as well as in concordance with FDA EUA (if applicable).

The guideline panel has developed a point-of-care clinical decision aid (Figure 5) to help prescribers identify the most appropriate treatment options for ambulatory patients with COVID-19. Prescribers can apply these guidelines by first identifying the baseline risk for severe outcomes for COVID-19 for their individual patient, such as need for hospitalization, non-invasive or invasive ventilation, progression to ICU care, or death. Table 1 lists conditions that are considered high-risk factors of progression to severe COVID-19 outcomes, and Table 2 lists other risk factors that may confer increased risk for severe COVID-19 outcomes. Patients may be considered "high risk" if they have one factor associated with high risk of progression or several factors associated with increased but not high risk of progression. If the patient does not have a high-risk condition or lacks a risk factor, the patient can be considered without risk factors for progression to severe disease.

When patients present with symptomatic mild to moderate COVID-19, the choice of antiviral therapy depends on several factors. These include overall effectiveness (i.e., absolute risk reduction), the certainty of underlying evidence, ease of administration (e.g., need for IV access or hospitalization), as well as patient-specific factors such as symptom duration, renal function, drug-drug interactions, and patient values and preferences.

Currently, there is not sufficient evidence to support combination antiviral treatment of mild to moderate COVID-19. Because nirmatrelvir/ritonavir has high efficacy and is administered orally, it should be the first option considered for ambulatory patients with mild to moderate COVID-19. While molnupiravir lacks

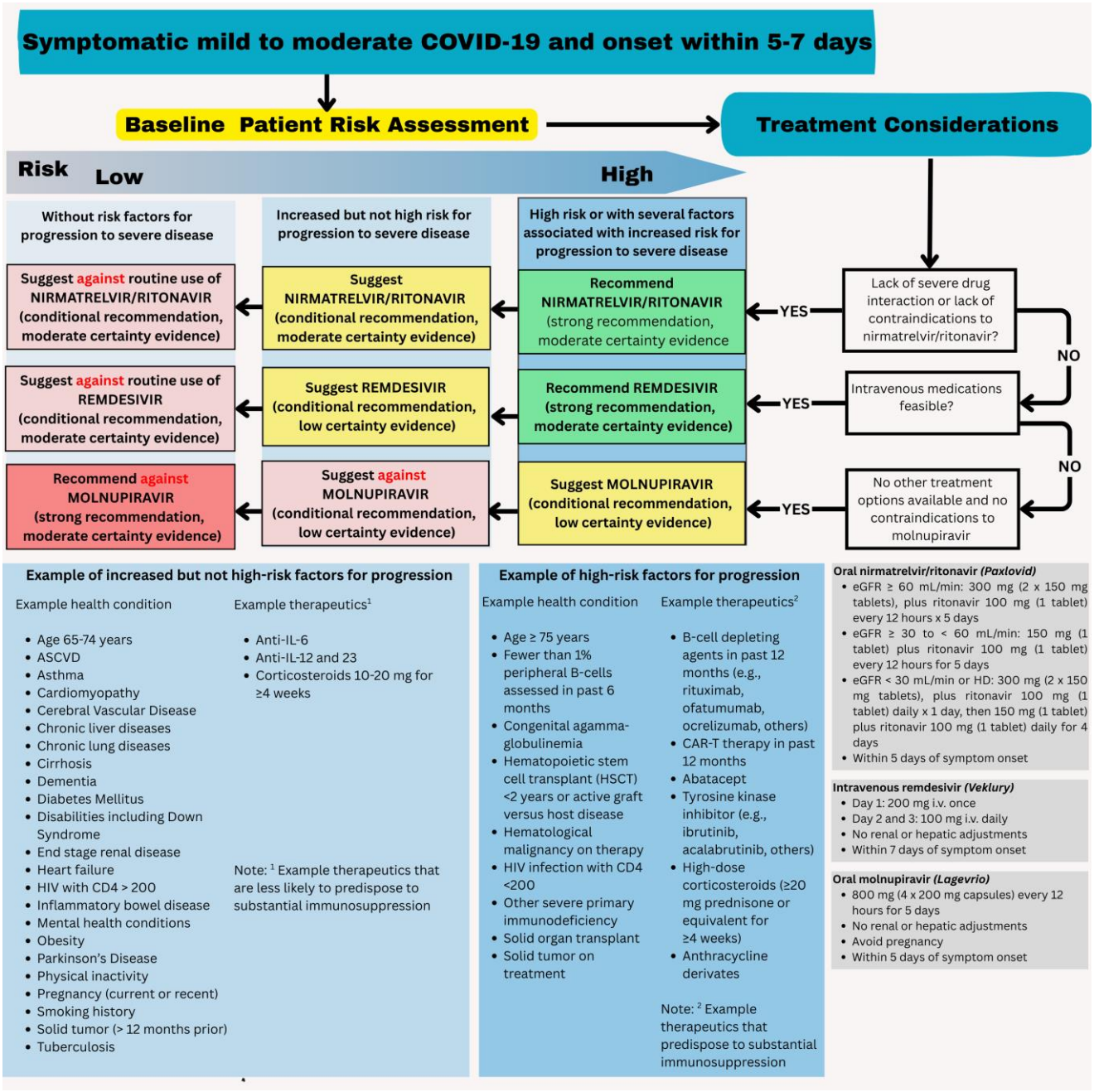
clinically significant drug-drug interactions, using it solely for convenience—without first evaluating whether nirmatrelvir/ritonavir or remdesivir can be used—is not recommended.

Ritonavir, one of the components of nirmatrelvir/ritonavir, is associated with numerous drug interactions. While it has been used in HIV management for nearly two decades and is supported by well-established guidance, nirmatrelvir/ritonavir is often prescribed in settings less familiar with ritonavir—such as primary care offices, urgent care centers, and emergency departments—where complete medication histories may not be readily available. Clinicians should carefully review the patient's full medication list and use tools such as www.covid19-druginteractions.org/checker, along with pharmacy input, to assess and manage interaction risks at the point of care.

Some patients may have drug-drug interactions that preclude the use of nirmatrelvir/ritonavir. For example, a patient with cardiovascular disease and recent coronary intervention may be taking clopidogrel and a statin. While the statin can be held during treatment, clopidogrel should not be co-administered with nirmatrelvir/ritonavir, as it reduces clopidogrel's effectiveness and may lead to poor outcomes such as restenosis. Another group at elevated risk for severe COVID-19 outcomes is transplant recipients on immunosuppressants like cyclosporine or tacrolimus. Co-administration of nirmatrelvir/ritonavir with these agents can lead to adverse events such as acute kidney injury or neurotoxicity due to their narrow therapeutic index. While transplant centers may be equipped to adjust calcineurin inhibitor doses, such monitoring may not be feasible in the outpatient settings where nirmatrelvir/ritonavir is often prescribed.

When nirmatrelvir/ritonavir is not a suitable option due to drug-drug interactions, remdesivir may be preferred. However, logistical barriers—such as the need for three consecutive days of IV infusion—can limit its feasibility. If neither option is available and the patient is at high risk for progression to severe disease (Table 1), molnupiravir may be considered, with clear communication about its uncertain benefits and potential concerns regarding mutagenicity and possible effects on fertility in individuals of childbearing potential.

Figure 5. Approaches to treatment of mild to moderate COVID-19



RESEARCH NEEDS AND FUTURE DIRECTIONS

With the emergence of newer variants and subvariants along with increasing immunity, it is difficult to be certain of the magnitude of decline of the risk for severe COVID-19 outcomes, which may also differ substantially across risk groups. Data on risk associated with specific risk conditions are heterogenous and often contradictory. Longitudinal, observational data on morbidity and mortality trends may help inform but is often fraught with confounding variables that limit the certainty of risk estimates. Researchers can help to mitigate some of these concerns by using standard definitions/criteria for high-risk conditions when describing the risk of severe COVID-19 outcomes in their research.

Newer antiviral agents are needed that overcome some of the limitations of current agents, such as drug-drug interactions, need for intravenous administration, or fertility/mutagenesis concerns. Ease of use is an important factor to ensure antiviral agents are appropriately utilized as evidence suggests that current antiviral agents are underprescribed in at risk populations [45,46].

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Drs. Adarsh Bhimraj and Rajesh T. Gandhi are chair and vice chair of the panel, respectively. The Non-hospitalized Patients subgroup, under the leadership of Dr. Amy Shumaker, led the development of the recommendations. Remaining panelists assisted with interpretation of data, as well as drafting, revising, and approving the recommendations and manuscript. Drs. Yngve Falck-Ytter, lead methodologist, and Rebecca Morgan, methodologist, were responsible for designing and performing the data analyses and leading the panel according to the GRADE process. Jennifer Loveless, methodologist, was responsible for project planning and management, including revisions to and final approval of the recommendations and manuscript.

Disclaimer: It is important to recognize that guidelines cannot always account for individual variation among patients. They are assessments of current scientific and clinical information provided as an educational service; are not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is drafted and when it is published or read); should not be considered inclusive of all proper methods of care, or as a statement of the standard of care; do not mandate any course of medical care; and are not intended to supplant clinician judgment with respect to particular patients or situations. Whether to follow guidelines and to what extent is voluntary, with the ultimate determination regarding their application to be made by the clinician in the light of each patient's individual circumstances. While IDSA makes every effort to present accurate, complete, and reliable information, these guidelines are presented "as is" without any warranty, either express or implied. IDSA (and its officers, directors, members, employees, and agents) assume no responsibility for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with these guidelines or reliance on the information presented.

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Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Possible conflicts of interest. Evaluation of relationships as potential conflicts of interest is determined by a review process. The assessment of disclosed relationships for possible COIs is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). No panelists had COIs directly related to abatacept. The following panelists have scientific advisory/consultant roles not related to the topic of COVID-19 with indicated companies: R.B. with Merck and Gilead, E.D. with Gilead, D.G. with Merck and Gilead, S. S. with Pfizer (concluded), and P.T. with Merck. The following panelists have scientific advisory/consultant roles related to outpatient antivirals but not nirmatrelvir/ritonavir, remdesivir, or molnupiravir with indicated companies: R.B. with Shionogi, K.C. with Pardes Biosciences (concluded), A.K. with Shionogi, S.S. with Adamis and Immunome (concluded), and P.T. with Shionogi. E.D. and K.C. have non-financial COIs related to ensitrelvir and nirmatrelvir/ritonavir, respectively. K.C.'s participation was carefully managed during discussions, and she recused from all voting. No disclosures were reported for all other authors (the majority of panelists), including chair and vice chair.

Additional Information: More detailed information on the analysis and development of the recommendation is available in the Supplementary Material.

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