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## LETTER TO THE EDITOR

# Outpatient Treatment of Confirmed COVID-19 in Symptomatic Adults: A Clinical Update Based on American College of Physicians Practice Points (Version 3, published online in February 2026)

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**Abstract**

***Background: Outpatient management of coronavirus disease 2019 (COVID-19) focuses on preventing progression to severe illness in high-risk individuals. The American College of Physicians (ACP) provides living, rapid practice points to guide antiviral use in symptomatic adults.***

***Objective: To summarize the 2026 ACP Practice Points (Version 3) for outpatient treatment of confirmed mild-to-moderate COVID-19.***

***Methods: This clinical update is based on ACP practice points and the accompanying living rapid review, incorporating evidence from randomized controlled trials and observational studies conducted during the SARS-CoV-2 Omicron variant period.***

***Results: ACP suggests considering nirmatrelvir–ritonavir and molnupiravir in symptomatic adults with mild-to-moderate COVID-19 who are within 5 days of symptom onset and at high risk for progression. Nirmatrelvir–ritonavir may improve recovery and reduce time to recovery, with cumulative evidence supporting reductions in hospitalization and mortality. Molnupiravir probably improves recovery and reduces persistent symptoms but likely does not reduce hospital admissions. ACP recommends against the use of ivermectin and sotrovimab.***

***Conclusion: Current ACP guidance supports selective use of oral antivirals in high-risk outpatients with early COVID-19. Clinical decision-making should be individualized, with attention to drug-drug interactions and patient-specific risk factors.***

***Keywords: COVID-19, outpatient treatment, antiviral therapy, nirmatrelvir-ritonavir, molnupiravir, American College of Physicians***

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## Introduction

Coronavirus disease 2019 (COVID-19) continues to pose a global health challenge, with current management increasingly focused on outpatient care aimed at preventing progression to severe disease. Early antiviral therapy in high-risk individuals remains a key strategy.

The American College of Physicians (ACP) has developed living, rapid practice points for outpatient treatment of confirmed COVID-19 [1]. The 2026 update (Version 3) reflects evidence from the SARS-CoV-2 Omicron variant period and reaffirms prior recommendations without major changes[1]. The ACP has also retired this topic from living status, indicating that new evidence is unlikely to substantially change current recommendations. This article provides a focused clinical update derived directly from these practice points.

## Methods

This clinical update is based on the ACP Practice Points (Version 3) and the accompanying living rapid review conducted by the ACP Center for Evidence Reviews[1,2]. The evidence base includes randomized controlled trials and observational studies evaluating outpatient antiviral therapies in symptomatic adults with confirmed COVID-19 during the SARS-CoV-2 Omicron variant period[2]. Key outcomes assessed include recovery, time to recovery, hospitalization, mortality, and adverse events.

## Review

ACP Practice Points

Nirmatrelvir–Ritonavir

ACP suggests considering nirmatrelvir–ritonavir in symptomatic adults who have mild-to-moderate COVID-19,

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are within 5 days of symptom onset, and are at high risk for progression to severe disease[1]. Evidence suggests that nirmatrelvir–ritonavir may improve recovery and reduce time to recovery[2] and has cumulative evidence supporting reductions in hospitalization and mortality[1,2]. Evidence regarding adverse events from randomized trials is uncertain; however, observational data suggest a possible increase in adverse events compared to no treatment[2]. Clinicians must carefully review for significant drug-drug interactions due to CYP3A inhibition[1].

**Molnupiravir**

ACP suggests considering molnupiravir in symptomatic patients within 5 days of symptom onset and in patients at high risk for progression to severe disease[1]. Evidence suggests that molnupiravir probably improves recovery and reduces time to recovery[2], probably reduces persistent symptoms[2], and probably does not reduce hospital admissions[2]. There is likely no difference in serious adverse events compared to usual care[2]. Molnupiravir is not recommended during pregnancy due to potential fetal harm. Effective contraception is advised for the duration of treatment and for 4 days after the last dose. Breastfeeding should be avoided during treatment and for 4 days after the last dose[4].

**Therapies Not Recommended**

ACP recommends against the use of ivermectin and sotrovimab[1]. These therapies have not demonstrated clinical benefit in outpatient management during the SARS-CoV-2 Omicron variant period.

Therapies Without Recommendation

ACP did not issue recommendations for the following therapies: enstirelvir, favipiravir, and simontrelvir–ritonavir[1]. The available evidence demonstrated no benefit, no net benefit, or was insufficient to support clinical use[2]. No eligible studies were identified for lopinavir–ritonavir during the SARS-CoV-2 Omicron variant period[2].

**Clinical Considerations**

*Risk Stratification*

Treatment decisions should prioritize patients at high risk for progression. Increasing age is the strongest predictor of severe disease. Additional risk factors include cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes mellitus, obesity, malignancy, and smoking history[1,3]. No validated risk prediction tools are currently available; therefore, clinical judgment remains essential.

*Timing of Therapy*

Antiviral therapy should be initiated as early as possible, ideally within 5 days of symptom onset[1].

*Drug Safety and Interactions*

Nirmatrelvir–ritonavir requires careful medication reconciliation due to significant drug–drug interactions[1]. Molnupiravir is associated with potential fetal harm[4].

*Viral Rebound*

Rebound symptoms and recurrent positivity following nirmatrelvir–ritonavir have been reported[1].

**Discussion**

The ACP Version 3 update reinforces a targeted approach to outpatient COVID-19 treatment, focusing on high-risk patients who are most likely to benefit from antiviral therapy. Among available options, nirmatrelvir–ritonavir demonstrates broader clinical benefit, including reductions in hospitalization and mortality, whereas molnupiravir provides more modest benefits primarily related to symptom resolution[1,2].

The absence of benefit with ivermectin and sotrovimab underscores the importance of evidence-based prescribing[1]. Additionally, the lack of sufficient evidence for several newer antivirals highlights ongoing gaps in outpatient COVID-19 therapeutics[2].

The decision by ACP to retire this topic from living status suggests stability in the evidence base and a low likelihood of major changes in recommendations in the near future[1].

**Conclusions**

According to ACP Practice Points (Version 3), outpatient management of confirmed mild-to-moderate COVID-19 should prioritize early antiviral therapy in high-risk patients. Nirmatrelvir–ritonavir and molnupiravir remain the only suggested treatment options. Clinical decision-making should be individualized, incorporating patient risk factors, safety considerations, and potential drug interactions. Therapies such as ivermectin and sotrovimab should not be used in this setting.

**Conflicts of Interest**

The authors have declared that no competing interests exist.

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**Ethics Statement**
This article is a clinical update based on previously published data and does not involve human participants or patient-identifiable information. Ethical approval was not required.

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