CLINICAL GUIDELINE

Outpatient Treatment of Confirmed COVID-19: Living, Rapid Practice Points From the American College of Physicians (Version 2)

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Description: Evidence for the use of outpatient treatments in adults with confirmed COVID-19 continues to evolve with new data. This is version 2 of the American College of Physicians (ACP) living, rapid practice points focusing on 22 outpatient treatments for COVID-19, specifically addressing the dominant SARS-CoV-2 Omicron variant.

Methods: The Population Health and Medical Science Committee (formerly the Scientific Medical Policy Committee) developed this version of the living, rapid practice points on the basis of a living, rapid review done by the ACP Center for Evidence Reviews at Cochrane Austria at the University for Continuing Education Krems (Danube University Krems). This topic will be maintained as living and rapid by continually monitoring and assessing the impact of new evidence.

Practice Point 1: *Consider molnupiravir to treat symptomatic patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 5 days of the onset of symptoms and at a high risk for progressing to severe disease.*

Practice Point 2: *Consider nirmatrelvir–ritonavir combination therapy to treat symptomatic patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 5 days of the onset of symptoms and at a high risk for progressing to severe disease.*

Practice Point 3: *Do not use ivermectin to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.*

Practice Point 4: *Do not use sotrovimab to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.*

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Although COVID-19 is no longer a global health emergency according to the World Health Organization and Centers for Disease Control and Prevention, it remains an ongoing health issue for which evidence continues to emerge addressing clinical dilemmas, such as the choice of treatment (1, 2). Management of most adults with COVID-19, especially those with mild to moderate disease, is increasingly occurring in the outpatient setting due to the availability of treatment options. This version (version 2) of the American College of Physicians (ACP) Population Health and Medical Science Committee's (PHMSC) living, rapid practice points presents advice about the treatment of adults with confirmed COVID-19 in outpatient settings, regardless of SARS-CoV-2 vaccination status. Mutations of the SARS-CoV-2 virus are continuously emerging, and they affect how well treatments for COVID-19 work (3, 4). This version of the practice points evaluates evidence specific to the SARS-CoV-2 Omicron variant becoming the dominant variant of concern. Version 1 of these practice points was published on 29 November 2022 (5). **Appendix Table 1** (available at Annals.org) summarizes changes in the methods, and **Appendix Table 2** (available at Annals.org) summarizes changes in the practice point statements between version 1 and version 2. **Table 1** (6–15) and **Figures 1** and **2** (14, 16) summarize the current evidence.

The intended audience for these practice points includes clinicians, patients, the public, and public health officials.

See also:

Related article 1377

Web-Only
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Update Alerts: These practice points are based on a literature search through 2 March 2023. There is a plan for bimonthly literature surveillance, and the living, rapid review along with the practice points will be periodically updated.

Table 1. Evidence Summary for Treatment of Confirmed COVID-19 in Outpatient Settings (Version 2)

Treatments Studies (Patients), *n**	Outcomes†						
	All-Cause Mortality	**COVID-19–Specific Mortality**	**Recovery**	**Time to Recovery**	**Hospital Admissions Due to COVID-19**	**Serious Adverse Events**	**Adverse Events**
Treatments supported for the Omicron variant							
Antiviral treatments							
Molnupiravir vs. usual care/no treatment							
1 RCT ($n = 25\,783$)	↔ Probably no difference (8) ●●○	No evidence	↑ Probably improves by 62%‡ (8) ●●○	↓ Probably reduces by 6 d (8) ●●○	No evidence	↔ Probably no difference (8) ●●○	No evidence
1 cohort ($n = 54\,217$)	**?** Very uncertain (12) ○○○	No evidence	No evidence	No evidence	**?** Very uncertain (12) ○○○	No evidence	No evidence
Nirmatrelvir–ritonavir combination therapy vs. no treatment							
5 cohorts§ ($n =$ 16 529–699 848)	↓ Probably associated with a reduction ranging from 51% to 85%‡ (7, 10, 12) ●●○	No evidence	No evidence	No evidence	↓ Probably associated with a reduction ranging from 24% to 60%‡ (7, 11, 12) ●●○	No evidence	No evidence
Treatments not supported for the Omicron variant							
Antiparasitic treatments							
Ivermectin vs. placebo							
1 RCT ($n = 1344$)	**?** Very uncertain (9) ○○○	No evidence	No evidence	↔ Probably no difference (9) ●●○	No evidence	**?** Very uncertain (9) ○○○	↔ May be no difference (9) ●○○
Monoclonal antibodies							
Sotrovimab vs. no treatment							
1 cohort ($n = 5205$)	↔ May be no association (6) ●○○	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Treatments with evidence of net benefit for SARS-CoV-2 variants before the Omicron variant							
Antiviral treatments							
Remdesivir				No evidence			
Monoclonal antibodies							
Casirivimab–imdevimab combination therapy				No evidence			
Regdanvimab				No evidence			
Treatments with evidence of no net benefit for SARS-CoV-2 variants before the Omicron variant							
Antibiotic treatments							
Azithromycin				No evidence			
Antiparasitic treatments							
Chloroquine/hydroxychloroquine				No evidence			
Nitazoxanide				No evidence			
Antiviral treatments							
Lopinavir–ritonavir combination therapy				No evidence			

Continued on following page

Table 1–Continued

Treatments Studies (Patients), *n**	Outcomes†						
	All-Cause Mortality	COVID-19–Specific Mortality	Recovery	Time to Recovery	Hospital Admissions Due to COVID-19	Serious Adverse Events	Adverse Events
Other treatments							
Ciclesonide				No evidence			
Convalescent plasma				No evidence			
Fluvoxamine				No evidence			
New treatments (version 2) with no evidence for the Omicron variant							
Antiviral treatments							
Ensitrelvir				No evidence			
Favipiravir				No evidence			
Monoclonal antibodies							
Tixagevimab-cilgavimab combination therapy				No evidence			
Other treatments							
Camostat mesylate				No evidence			
Chlorpheniramine				No evidence			
Colchicine				No evidence			
Metformin				No evidence			
Niclosamide				No evidence			

RCT = randomized controlled trial.
* Total baseline sample sizes are reported. Analytic sample sizes may vary by outcome.
† ? very uncertain about the effect, ↑ effect increase, ↓ effect decrease, ↔ no difference in effect. Certainty of evidence: ○○○ = insufficient, any estimate of effect is very uncertain; ●○○ = low, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; ●●○ = moderate, further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; ●●● = high, further research is very unlikely to change our confidence in the estimate of effect (13).
‡ Percentages represent the risk reduction determined from the hazard, odds, and/or risk ratios for the individual studies included in the living, rapid review (version 2) (14).
§ One study evaluating nirmatrelvir–ritonavir combination therapy versus no treatment reported results by age groups only, thereby contributing only to results for key question 1a and not key question 1 reflected in this table (15).

Practice Points Development Process

An overview of the PHMSC as well as details of ACP's living and rapid development process, including signals for updating and retirement, and policy on disclosure of interests and management of conflicts of interest can be found in ACP's methods articles (17, 18). Bimonthly literature surveillance is planned to identify and evaluate new evidence from published literature that meets eligibility criteria to maintain this topic as rapid and living (17). Rather than specifying a set interval for issuing updates, the PHMSC will update these practice points when evidence emerges that the committee believes warrants a change in the clinical advice. The PHMSC may determine that a topic does not require further updates and, therefore, may decide to retire the publication from rapid or living status. The PHMSC will publish an update alert in the journal reporting the change in status along with a brief rationale.

Living, Rapid Review

These practice points are based on version 2 of a living, rapid review funded by ACP and conducted by the ACP Center for Evidence Reviews at Cochrane Austria at the University for Continuing Education Krems (Danube University Krems) to address the key questions (14). The search and inclusion criteria were modified to focus on the Omicron variant by limiting studies to only those enrolling patients on or after 26 November 2021, when the World Health Organization first described the Omicron variant (19, 20) (Appendix Table 1). None of the studies included in version 1 were eligible for inclusion in version 2 because of this new restriction.

Key Question 1: What are the benefits and harms of COVID-19 treatments in symptomatic and asymptomatic adult patients with a confirmed SARS-CoV-2 infection in the outpatient setting?

Key Question 1a: Do the benefits and harms vary by patient characteristics (age, gender, socioeconomic status, or comorbid conditions), type of SARS-CoV-2 variant, immunity status (prior SARS-CoV-2 infection, vaccination status, or time since infection or vaccination), symptom duration, or disease severity?

Treatments Evaluated

The living, rapid review (14) evaluated the following treatments for which advice is most needed to inform clinical decision making (an asterisk indicates newly added treatments since version 1). Some treatments may be used in the inpatient setting or as adjunctive therapies in practice. However, the living, rapid review only included studies if the treatment was the primary treatment that patients received in the outpatient setting.

- Niclosamide* (anthelmintic)
- Azithromycin (antibiotic)
- Colchicine* (antigout agent)
- Chlorpheniramine* (antihistamine)

Figure 1. Evidence summary for treatment of confirmed COVID-19 in outpatient settings.

ACP American College of Physicians
Leading Internal Medicine, Improving Lives

Living, Rapid Practice Points
Version 2
Approved June 2023

Outpatient Treatments for Confirmed COVID-19

Population: Adults in the Outpatient Setting

Eligible Studies: 2 Randomized Trials; 6 Cohort Studies

Comparison: Placebo, Usual Care, No Treatment

Total Sample Size = 1 149 939
Sample Size Range: 1344 to 699 848

Risk of Bias:
5 Moderate and 3 High

Evidence Supports Use for the SARS-CoV-2 Omicron Variant

Treatment Trials; Sample Size*	All-Cause Mortality	COVID-19 Mortality	Recovery	Time to Recovery	COVID-19 Hospital Admission	Serious Adverse Events	Adverse Events
Molnupiravir 1 RCT; *n* = 25 783 1 Cohort; *n* = 54 217	Probably no difference ↔ ●●○†	No evidence	Probably improves ↑ ●●○	Probably reduces ↓ ●●○	Very uncertain ? ○○○	Probably no difference ↔ ●●○	No evidence
Nirmatrelvir–Ritonavir 5 Cohorts; *n* = 16 529 to 699 848	Probably reduces ↓ ●●○	No evidence	No evidence	No evidence	Probably reduces ↓ ●●○	No evidence	No evidence

Evidence Does Not Support Use for the SARS-CoV-2 Omicron Variant

Ivermectin 1 RCT; *n* = 1344	Very uncertain ? ○○○	No evidence	No evidence	Probably no difference ↔ ●●○	No evidence	Very uncertain ? ○○○	May be no difference ↔ ●○○
Sotrovimab 1 Cohort; *n* = 5205	May be no association ↔ ●○○	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence

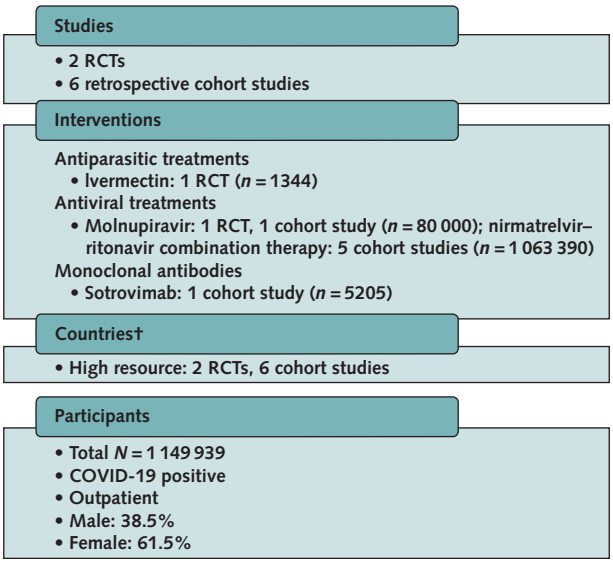
Note. Before initiating COVID-19 treatment, review treatment warnings and precautions, as well as all medications and potential drug interactions.
* Total baseline sample sizes are reported. Analytic sample sizes might vary by outcome. † Evidence from 1 cohort study was insufficient.
CoE ratings: High CoE ●●● Moderate CoE ●●○ Low CoE ●○○ Insufficient CoE ○○○

Treatments With No Evidence for the SARS-CoV-2 Omicron Variant

New treatments in Version 2 with no evidence for the SARS-CoV-2 Omicron variant	Camostat mesylate, chlorpheniramine, colchicine, ensitrelvir, favipiravir, metformin, niclosamide, and tixagevimab–cilgavimab
Treatments in Version 1 with evidence of net benefit before the SARS-CoV-2 Omicron variant	Casirivimab–imdevimab, regdanvimab, and remdesivir
Treatments in Version 1 with evidence of no net benefit before the SARS-CoV-2 Omicron variant	Azithromycin, chloroquine/hydroxychloroquine, ciclesonide, convalescent plasma, fluvoxamine, lopinavir–ritonavir, and nitazoxanide

CoE = certainty of evidence; RCT = randomized controlled trial.

Figure 2. Evidence description*.



ACP = American College of Physicians; RCT = randomized controlled trial.
* Evidence search and assessment done by the ACP Center for Evidence Reviews at Cochrane Austria at the University for Continuing Education Krems (Danube University Krems) (14). A search for evidence from 26 November 2021 to 2 March 2023 aimed to identify RCTs and cohort studies evaluating select primary treatment of persons with COVID-19 in the outpatient setting.
† See reference 16.

- Chloroquine or hydroxychloroquine, ivermectin, and nitazoxanide (antiparasitics)
- Ensitrelvir*, favipiravir*, lopinavir–ritonavir combination therapy, molnupiravir, nirmatrelvir–ritonavir combination therapy, and remdesivir (antivirals)
- Metformin* (biguanide)
- Convalescent plasma
- Corticosteroids
- Casirivimab–imdevimab combination therapy, regdanvimab, sotrovimab, and tixagevimab–cilgavimab combination therapy* (monoclonal antibodies approved by the U.S. Food and Drug Administration or European Medicines Agency for treatment of COVID-19 as of 2 March 2023)
- Camostat mesylate* (protease inhibitor)
- Fluvoxamine (selective serotonin reuptake inhibitor)

Outcomes of Interest

The PHMSC reviewed core outcome sets for COVID-19 (21–24) and rated the following outcomes as critical: all-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospital admissions due to COVID-19, serious adverse events, and adverse events. There was no change in the outcomes evaluated from version 1 to version 2.

Summary of New Evidence

Table 1 summarizes the evidence for version 2 of the living, rapid review (14). Two randomized controlled trials were identified that compared treatments with placebo (9) or usual care (8), as well as 6 retrospective cohort studies that compared treatments with no treatment (6, 7, 10–12, 15). Of the 22 eligible treatments for version 2 of the practice points, only 4 have evidence that specifically addressed the Omicron variant: ivermectin (1 study [9]), molnupiravir (2 studies [8, 12]), nirmatrelvir–ritonavir combination therapy (5 studies [7, 10–12, 15]), and sotrovimab (1 study [6]). Of the 8 included studies, 5 were fair quality (6, 8, 10, 11, 15) and 3 were poor quality (7, 9, 12). Coronavirus disease 2019 was confirmed by diagnostic testing, usually a reverse transcriptase polymerase chain reaction or antigen test; when a test result was unavailable, a diagnosis code for COVID-19 or the order date for the treatment being studied was used as a proxy for COVID-19 diagnosis. None of the new studies reported enrolling patients on the basis of SARS-CoV-2 vaccination status or prior diagnosis of COVID-19. In studies providing information, the percentage of patients who were fully vaccinated (depending on country and time of study enrollment) ranged from 13% to 94%, and the percentage of patients with previous self-reported COVID-19 ranged from 7% to 15%. Among the 8 new studies, 2 (8, 9) included only symptomatic patients and 6 included patients within 5 days of symptom onset (7, 10–12, 15) or with early symptoms (6). In 6 of these studies, only patients with documented underlying conditions (11), patients with relevant comorbidities (8), or patients at risk for progression to severe disease (7, 10, 12, 15) were eligible to participate. Further, 3 of these studies explicitly reported enrolling patients on the basis of having mild (12) or mild to moderate COVID-19 (7, 11).

There were 5 new studies that informed key question 1a about the variability in benefits and harms based on patient characteristics and immunity status (8, 10–12, 15). Symptom duration and disease severity were not evaluated in the new studies, and type of SARS-CoV-2 variant was not applicable because this version of the practice points focused on the Omicron variant. We could not draw conclusions about how to tailor treatment advice to certain risk groups due to inconsistency in the studies (14).

Practice Points and Rationales (Version 2)

The practice points and new evidence are summarized in Table 1 and Figures 1 and 2. The practice points are primarily informed by evidence evaluating the predominance of the Omicron variant (14) while considering the evidence from version 1 of the living, rapid review (25) and contextual considerations, such as the availability of treatments. Table 2 (26, 27) provides the current dosage of supported treatment options from the U.S. Food and Drug Administration.

Treatments Supported for the Omicron Variant

The order in which treatments are listed does not imply prioritization for outpatient treatment of COVID-19.

Table 2. Dosages for Treatment Options*

Antivirals	Dosages
Molnupiravir (26)	800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days
Nirmatrelvir–ritonavir combination therapy (27)	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days *Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days*

eGFR = estimated glomerular filtration rate.
* Based on information available as of 21 August 2023.

Antiviral Treatments

Practice Point 1: Consider molnupiravir to treat symptomatic patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 5 days of the onset of symptoms and at a high risk for progressing to severe disease.

New evidence for the Omicron variant suggests a net benefit of molnupiravir in patients for whom treatment is initiated within 5 days of symptom onset, which is consistent with version 1 of the practice points. New evidence showed that molnupiravir probably improves recovery and reduces time to recovery compared with usual care (moderate certainty). However, there is probably no difference in all-cause mortality (moderate certainty). Evidence for harms showed that there is probably no difference in the incidence of serious adverse events (moderate certainty). Evidence is very uncertain or lacking for other critical outcomes.

Practice Point 2: Consider nirmatrelvir–ritonavir combination therapy to treat symptomatic patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 5 days of the onset of symptoms and at a high risk for progressing to severe disease.

New evidence for the Omicron variant suggests a net benefit of nirmatrelvir–ritonavir combination therapy in patients for whom treatment is initiated within 5 days of symptom onset, which is consistent with version 1 of the practice points. New evidence showed that nirmatrelvir–ritonavir combination therapy is probably associated with a reduction in all-cause mortality and hospital admissions due to COVID-19 compared with no treatment (moderate certainty). Evidence is lacking for other critical outcomes including harms.

Treatments Not Supported for the Omicron Variant

Antiparasitic Treatments

Practice Point 3: Do not use ivermectin to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

New evidence for the Omicron variant is consistent with version 1 of the practice points that there is no net benefit of using ivermectin to treat COVID-19. New evidence showed that there is probably no difference in time to recovery (moderate certainty) and that there may be no difference in the incidence of adverse events (low certainty) for ivermectin compared with placebo. Evidence is very uncertain for all-cause mortality and serious adverse events and is lacking for other critical outcomes.

Monoclonal Antibodies

Practice Point 4: Do not use sotrovimab to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

New evidence adds to information that sotrovimab is not effective against the Omicron variant (28). New evidence showed no net benefit; sotrovimab may not be associated with all-cause mortality compared with no treatment (low certainty). Evidence is lacking for other critical outcomes, including harms.

Treatments With Evidence of Net Benefit for SARS-CoV-2 Variants Before the Omicron Variant

Antiviral Treatments

Remdesivir. No eligible studies evaluated the benefits and harms of remdesivir for the Omicron variant. Evidence from version 1 showed a net benefit of remdesivir as it may improve recovery and reduce hospital admissions due to COVID-19 (low certainty) with probably no difference from placebo in the incidence of adverse events (moderate certainty) before Omicron became the dominant SARS-CoV-2 variant. Therefore, clinicians should prioritize the use of other available treatments that show effectiveness against the Omicron variant.

Monoclonal Antibodies

Casirivimab–Imdevimab Combination Therapy. No eligible studies evaluated the benefits and harms of casirivimab–imdevimab combination therapy for the Omicron variant. There was evidence of a net benefit of casirivimab–imdevimab combination therapy compared with placebo (reductions in time to recovery [high certainty] and hospital admissions due to COVID-19 [moderate certainty]) in version 1. Because monoclonal antibodies target the spike protein of the virus and the efficacy of using monoclonal antibody treatment for COVID-19 varies depending on the SARS-CoV-2 variant, Omicron and its subvariants are not expected to be susceptible to casirivimab–imdevimab combination therapy (28). Therefore, clinicians should prioritize the use of other available treatments that show effectiveness against the Omicron variant.

Regdanvimab. No eligible studies evaluated the benefits and harms of regdanvimab for the Omicron variant. Despite evidence of a net benefit of regdanvimab compared with placebo (improvement in recovery [moderate certainty] with no difference in the incidence of

adverse events [low certainty]) in version 1, monoclonal antibodies target the spike protein of the virus, and the susceptibility of regdanvimab to Omicron and its subvariants is uncertain. Therefore, clinicians should prioritize the use of other available treatments that show effectiveness against the Omicron variant.

Treatments With Evidence of No Net Benefit for SARS-CoV-2 Variants Before the Omicron Variant

Antibiotic Treatments

Azithromycin. No eligible studies evaluated the benefits and harms of azithromycin for the Omicron variant. In version 1, evidence showed that harms outweighed no benefit of using azithromycin to treat COVID-19.

Antiparasitic Treatments

Chloroquine or Hydroxychloroquine. No eligible studies evaluated the benefits and harms of chloroquine or hydroxychloroquine for the Omicron variant. In version 1, evidence showed that there was no net benefit of using hydroxychloroquine to treat COVID-19. Evidence was lacking in version 1 about the efficacy of chloroquine for all critical outcomes.

Nitazoxanide. No eligible studies evaluated the benefits and harms of nitazoxanide for the Omicron variant. In version 1, evidence showed that there was no net benefit of using nitazoxanide to treat COVID-19.

Antiviral Treatments

Lopinavir–Ritonavir Combination Therapy. No eligible studies evaluated the benefits and harms of lopinavir–ritonavir combination therapy for the Omicron variant. In version 1, evidence showed that harms outweighed no benefit of using lopinavir–ritonavir combination therapy to treat COVID-19.

Other Treatments

Ciclesonide. No eligible studies evaluated the benefits and harms of ciclesonide for the Omicron variant. In version 1, evidence showed that there was no net benefit of using inhaled or intranasal ciclesonide to treat COVID-19.

Convalescent Plasma. No eligible studies evaluated the benefits and harms of convalescent plasma for the Omicron variant. In version 1, evidence showed that there was no net benefit of using convalescent plasma to treat COVID-19.

Fluvoxamine. No eligible studies evaluated the benefits and harms of fluvoxamine for the Omicron variant. In version 1, evidence showed that there was no net benefit of using fluvoxamine to treat COVID-19.

New Treatments (Version 2) With No Evidence for the Omicron Variant

There were no eligible studies evaluating the benefits and harms of the following new treatments (version 2 only) for the Omicron variant.

Antivirals

- Ensitrelvir
- Favipiravir

Monoclonal Antibodies

- Tixagevimab–cilgavimab combination therapy

Other Treatments

- Camostat mesylate
- Chlorpheniramine
- Colchicine
- Metformin
- Niclosamide

CLINICAL CONSIDERATIONS

- The living, rapid review did not evaluate comparative effectiveness, meaning evidence does not show if one treatment is more effective than another treatment.
- Risk stratification is an important step in the initial evaluation to decide the best approach to treatment of COVID-19 in the outpatient setting. The current definition of risk factors for progression to severe COVID-19 disease can be accessed from the Centers for Disease Control and Prevention's website: www.cdc.gov/coronavirus/2019-ncov/your-health/risks-getting-very-sick.html.
- Outpatient management of mild to moderate COVID-19 is appropriate for most patients. The decision to initiate treatment for COVID-19 in the outpatient setting should be personalized and based on clinical judgment using an informed decision-making approach with the patient on potential treatment benefits, harms, patient characteristics (such as risk factors, comorbid conditions, and disease severity), patient preferences, and social determinants of health.
- Before initiating outpatient treatment for COVID-19, review treatment warnings and precautions as well as all medications and potential drug interactions.
- Viral rebound of SARS-CoV-2 and the recurrence of COVID-19 symptoms have been reported in some patients completing treatment with nirmatrelvir–ritonavir combination therapy (29).

EVIDENCE GAPS

- More research evaluating the efficacy, effectiveness, and comparative effectiveness, as well as harms, of pharmacologic and biologic treatments of COVID-19 in the outpatient setting is needed, particularly in the context of changing dominant SARS-CoV-2 variants and subvariants.
- The effectiveness of retreatment of COVID-19 in patients with previous infections is an area that requires further research.
- Studies applying prespecified subgroup analyses are needed to assess whether the efficacy and effectiveness of treatments for COVID-19 used in the outpatient setting vary by patient characteristics (age, gender, socioeconomic status, or comorbid conditions), type

of SARS-CoV-2 variant, immunity status (prior SARS-CoV-2 infection, vaccination status, or time since infection or vaccination), symptom duration, or disease severity.

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Note: The practice points are meant to guide care based on the best available evidence and may not apply to all patients or individual clinical situations. They should not be used as a replacement for a clinician's judgment. Any reference to a product or process contained in a practice point is not intended as an endorsement of any specific commercial product. All practice points are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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Author contributions are available at Annals.org.

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Appendix Table 1. What Has Changed Since the Last Version—Methods

Methods	Version 1	Version 2
Key questions	Subgroups of interest for key question 1a: age, gender, and comorbid conditions	Added socioeconomic status as a subgroup of interest for key question 1a
Inclusion criteria: study design	Only included RCTs with no restriction on enrollment date	Added prospective and retrospective cohort studies as designs of interest that met the following criteria: • Sample size ≥5000 • Adjusted for all the following confounding factors: age, comorbid conditions, and vaccination status. RCTs and cohort studies enrolling participants on or after 26 November 2021 to focus on the SARS-CoV-2 Omicron variant
Inclusion criteria: treatments evaluated	Included: • Azithromycin (antibiotic) • Chloroquine or hydroxychloroquine, ivermectin, and nitazoxanide (antiparasitics) • Lopinavir–ritonavir combination therapy, molnupiravir, nirmatrelvir–ritonavir combination therapy, and remdesivir (antivirals) • Convalescent plasma • Corticosteroids • Bebtelovimab, casirivimab–imdevimab combination therapy, regdanvimab, sotrovimab (monoclonal antibodies) • Fluvoxamine (selective serotonin reuptake inhibitor)	Added: • Niclosamide (anthelmintic) • Colchicine (antigout agent) • Chlorpheniramine (antihistamine) • Ensitrelvir, favipiravir (antivirals) • Metformin (biguanide) • Tixagevimab–cilgavimab combination therapy (monoclonal antibody) • Camostat mesylate (protease inhibitor) Removed: • Bebtelovimab (monoclonal antibody)
Inclusion criteria: comparisons	The only comparison was placebo	Added no treatment or usual care as comparisons

RCT = randomized controlled trial.

Appendix Table 2. What Has Changed Since the Last Version—Practice Points

Treatments	Version 1: Evidence Before the SARS-CoV-2 Omicron Variant	Version 2: Evidence for the SARS-CoV-2 Omicron Variant
Antibiotic treatments		
Azithromycin	Not supported	No eligible studies
Antiviral treatments		
Ensitrelvir	Not evaluated	No eligible studies
Favipiravir	Not evaluated	No eligible studies
Lopinavir–ritonavir combination therapy	Not supported	No eligible studies
Molnupiravir	Supported	Supported
Nirmatrelvir–ritonavir combination therapy	Supported	Supported
Remdesivir	Supported	No eligible studies
Antiparasitic treatments		
Chloroquine/hydroxychloroquine	Not supported	No eligible studies
Ivermectin	Not supported	Not supported
Nitazoxanide	Not supported	No eligible studies
Monoclonal antibodies		
Bebtelovimab	No eligible studies	Not evaluated
Casirivimab–imdevimab combination therapy	Supported if considered effective against a SARS-CoV-2 variant or subvariant locally in circulation	No eligible studies
Regdanvimab	Supported if considered effective against a SARS-CoV-2 variant or subvariant locally in circulation	No eligible studies
Sotrovimab	Supported if considered effective against a SARS-CoV-2 variant or subvariant locally in circulation	Not supported
Tixagevimab–cilgavimab combination therapy	Not evaluated	No eligible studies
Other treatments		
Camostat mesylate	Not evaluated	No eligible studies
Chlorpheniramine	Not evaluated	No eligible studies
Ciclesonide	Not supported	No eligible studies
Colchicine	Not evaluated	No eligible studies
Convalescent plasma	Not supported	No eligible studies
Fluvoxamine	Not supported	No eligible studies
Metformin	Not evaluated	No eligible studies
Niclosamide	Not evaluated	No eligible studies