Outpatient Treatment of Confirmed COVID-19: Living, Rapid Practice Points From the American College of Physicians (Version 1)

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**Description:** Strategies to manage COVID-19 in the outpatient setting continue to evolve as new data emerge on SARS-CoV-2 variants and the availability of newer treatments. The Scientific Medical Policy Committee (SMPC) of the American College of Physicians (ACP) developed these living, rapid practice points to summarize the best available evidence on the treatment of adults with confirmed COVID-19 in an outpatient setting. These practice points do not evaluate COVID-19 treatments in the inpatient setting or adjunctive COVID-19 treatments in the outpatient setting.

**Methods:** The SMPC developed these 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). The SMPC will maintain these practice points as living by monitoring and assessing the impact of new evidence.

**Practice Point 1:** Consider molnupiravir to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 5 to 7 days of the onset of symptoms and at high risk for progressing to severe disease.

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

**Practice Point 3:** Consider remdesivir to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 7 days of the onset of symptoms and at high risk for progressing to severe disease.

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

**Practice Point 5:** Do not use chloroquine or hydroxychloroquine to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

**Practice Point 6:** Do not use ivermectin to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

**Practice Point 7:** Do not use nitazoxanide to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

**Practice Point 8:** Do not use lopinavir-ritonavir combination therapy to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

**Practice Point 9:** Do not use casirivimab-imdevimab combination therapy to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting unless it is considered effective against a SARS-CoV-2 variant or subvariant locally in circulation.

**Practice Point 10:** Do not use regdanvimab to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting unless it is considered effective against a SARS-CoV-2 variant or subvariant locally in circulation.

**Practice Point 11:** Do not use sotrovimab to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting unless it is considered effective against a SARS-CoV-2 variant or subvariant locally in circulation.

**Practice Point 12:** Do not use convalescent plasma to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

**Practice Point 13:** Do not use ciclesonide to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

**Practice Point 14:** Do not use fluvoxamine to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

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**Update Alerts:** These practice points are based on a literature search through 4 April 2022. There is a plan for monthly literature surveillance, and the living, rapid review along with the practice points will be periodically updated.
The COVID-19 pandemic continues to be a global health priority, and most COVID-19 illness occurs in the outpatient setting. Because of reductions in the risk for severe COVID-19—largely due to vaccination and the Omicron variant and subvariants (which are generally associated with less severe illness although are more highly transmissible than prior strains) (1), as well as an increase in treatment options—patients with COVID-19 are increasingly treated in the outpatient setting (2). In addition to vaccination, prevention of the development of serious illness will be the most relevant step for reducing morbidity and mortality associated with COVID-19. The Scientific Medical Policy Committee (SMPC) of the American College of Physicians (ACP) developed these living, rapid practice points to provide clinical advice based on the best available evidence about the treatment of adults with confirmed COVID-19 in the outpatient setting.

**Scope and Purpose**

The SMPC developed version 1 of these living, rapid practice points to summarize the best available evidence about the use of pharmacologic and biologic treatments of COVID-19 in the outpatient setting. These practice points do not address the use of COVID-19 treatments in the inpatient setting or adjunctive treatments of COVID-19 in the outpatient setting. Table 1 and Figures 1 and 2 summarize the current evidence (3-31).

**Population**

The population is all adult patients diagnosed with COVID-19 in the outpatient setting regardless of SARS-CoV-2 vaccination status.

**Intended Audience**

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

**Practice Points Development Process**

The SMPC developed these practice points according to ACP’s methods for the rapid development of practice points and policy on disclosure of interests and management of conflicts of interest. The SMPC intends to maintain this topic as living. Monthly literature surveillance is planned to identify and evaluate new evidence. Surveillance through 17 August 2022 identified 6 new studies since the initial search date, which are described in the living, rapid review (31). Evidence is rapidly evolving, and studies published after the initial search date that meet inclusion criteria will be incorporated into periodic updates and future versions of both the practice points and the review.

**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, 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 following treatments for adults with confirmed COVID-19 in the outpatient setting were identified by the SMPC, in consultation with the ACP Center for Evidence Reviews, as those for which clinical advice was most needed to inform decision making. In practice, some treatments might be used as adjunctive therapies. However, studies were included in the living, rapid review only if the treatment was the primary treatment that patients received.

- Antibiotics: azithromycin
- Antiparasitics: chloroquine or hydroxychloroquine, ivermectin, and nitazoxanide
- Antivirals: lopinavir–ritonavir combination therapy, molnupiravir, nirmatrelvir–ritonavir combination therapy, and remdesivir
- Convalescent plasma
- Corticosteroids: ciclesonide
- Fluvoxamine (selective serotonin reuptake inhibitor)
- Monoclonal antibodies approved by the U.S. Food and Drug Administration or European Medicines Agency as of 4 April 2022: bebtelovimab, casirivimab–imdevimab combination therapy, regdanvimab, and sotrovimab

**Outcomes of Interest**

The SMPC reviewed core outcome sets for COVID-19 (34-37) 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.

**Overview of the Evidence**

The living, rapid review (31) identified 26 placebo-controlled randomized studies informing key question 1

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**Table 1**

| Treatments Evaluated | Outcomes of Interest |
|----------------------|----------------------|
| Antibiotics          | All-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospital admissions due to COVID-19, serious adverse events, and adverse events |
| Antiparasitics        | All-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospital admissions due to COVID-19, serious adverse events, and adverse events |
| Antivirals            | All-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospital admissions due to COVID-19, serious adverse events, and adverse events |
| Convalescent plasma  | All-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospital admissions due to COVID-19, serious adverse events, and adverse events |
| Corticosteroids       | All-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospital admissions due to COVID-19, serious adverse events, and adverse events |
| Fluvoxamine           | All-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospital admissions due to COVID-19, serious adverse events, and adverse events |
| Monoclonal antibodies | All-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospital admissions due to COVID-19, serious adverse events, and adverse events |
### Table 1. Evidence Summary for Treatment of Confirmed COVID-19 in Outpatient Settings (Version 1)

| Treatments | Studies (Patients), n* | All-Cause Mortality | COVID-19-Specific Mortality | Recovery | Time to Recovery | Hospital Admissions due to COVID-19 | Serious Adverse Events | Adverse Events |
|------------|-----------------------|---------------------|-----------------------------|----------|-----------------|------------------------------------|------------------------|---------------|
| **Antibiotics** | | | | | | | | |
| Azithromycin vs. placebo | 1 RCT (n = 263) | ? | Very uncertain (17) | No evidence | May be no difference (17) | No evidence | ? | Very uncertain (17) | May increase (17) |
| Hydroxychloroquine vs. placebo | 3 RCTs (n = 148 to 456) | ? | Very uncertain (18, 20, 23) | ? | Very uncertain (18, 23) | ? | ? | ? | ? |
| Ivermectin vs. placebo | 5 RCTs (n = 24 to 1358) | May be no difference (4, 5, 16, 28) | ? | ? | ? | ? | ? | ? |
| Nitazoxanide vs. placebo | 2 RCTs (n = 475 to 1092) | ? | Very uncertain (21, 22) | ? | ? | ? | ? | ? |
| **Antivirals** | | | | | | | | |
| Lopinavir-ritonavir vs. placebo | 1 RCT (n = 471) | Very uncertain (20) | No evidence | No evidence | No evidence | May be no difference (20) | ? | ? |
| Molnupiravir vs. placebo | 2 RCTs (n = 204 to 1433) | May reduce (11) | ? | ? | ? | ? | ? | ? |
| Nirmatrelvir-ritonavir vs. placebo | 1 RCT (n = 2246) | ? | Probably reduces (10) | ? | ? | ? | ? | ? |
| Remdesivir vs. placebo | 1 RCT (n = 584) | ? | Very uncertain (8) | No evidence | May improve (8) | No evidence | ? | Very uncertain (8) | Probably no difference (8) |
| **Monoclonal antibodies** | | | | | | | | |
| Casirivimab-imdevimab vs. placebo | 1 RCT (n = 5607) | ? | Very uncertain (27) | No evidence | No evidence | Reduces (27) | ? | Very uncertain (27) |
| Regdanvimab vs. placebo | 2 RCTs (n = 18 to 327) | Very uncertain (24) | No evidence | ? | ? | ? | ? | ? |
| Sotrovimab vs. placebo | 1 RCT (n = 1057) | ? | Very uncertain (9) | No evidence | No evidence | May reduce (9) | ? | Very uncertain (9) | Probably no difference (9) |
| **Other treatments** | | | | | | | | |
| Convalescent plasma vs. placebo | 4 RCTs (n = 160 to 1225) | May be no difference (13, 15, 25, 29) | ? | ? | ? | ? | ? | ? |
| Ciclesonide vs. placebo | 1 RCT (n = 215) | Very uncertain (6) | ? | ? | ? | ? | ? | ? |

*Continued on following page*
about the benefits and harms of treatment options (4-29). Only 1 of these studies (19) informed key question 1a about variability in benefits and harms. Studies included in the review were limited to placebo-controlled trials that evaluated efficacy or how well the treatments work in controlled circumstances because no standard of care had been established for COVID-19 in the outpatient setting.

**Practice Points and Rationale**

Table 1 and Figures 1 and 2 summarize the practice points and evidence. The practice points consider the best available, appraised evidence. Outpatient treatment of COVID-19 should generally be considered only in patients with confirmed mild to moderate COVID-19.

Current definitions of the categories of COVID-19 severity (asymptomatic, mild, moderate, severe, and critical) can be accessed on the website of the Centers for Disease Control and Prevention (www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum) (38). Determining the best approach to treatment of COVID-19 in the outpatient setting should be a personalized decision based on clinical judgment, discussion, and shared decision making with the patient about potential treatment benefits, harms, patient characteristics (such as risk factors, comorbid conditions, and disease severity), and patient preferences. Table 2 provides the current dosages of treatment options from the Food and Drug Administration and European Medicines Agency.

**Applicability**

All studies were done before the Omicron variant became the dominant circulating strain. In all of the included studies, COVID-19 was confirmed by diagnostic testing, usually a reverse transcriptase polymerase chain reaction test. Eleven of the 26 included studies excluded patients who were vaccinated (6-8, 10, 11, 13, 18, 19, 24, 27, 29), 5 excluded patients who had been previously diagnosed with COVID-19 (10, 12, 22, 25, 29), and 1 included patients if they had not been hospitalized or treated for COVID-19 (8). The duration of symptoms before study entry varied; overall, patients had had symptoms for shorter than 12 days. Only 1 of the included studies explicitly reported that patients were not required to be symptomatic for study entry (17). The way in which the included studies in the living, rapid review were done (for example, enrollment criteria and data analysis) did not allow conclusions to be drawn about how the efficacy and harms of treatment vary with such factors as patient characteristics (for example, age, gender, and comorbid conditions), SARS-CoV-2 variants and subvariants, immunity status (for example, prior SARS-CoV-2 infection, vaccination status, and time since infection or vaccination), symptom duration, and COVID-19 severity. Ongoing literature surveillance is planned to identify any relevant new studies, including those evaluating future SARS-CoV-2 variants of concern that have yet to emerge.

**Treatments Supported**

The following treatments are listed alphabetically, and the order does not imply prioritization for outpatient treatment of COVID-19.

**Antiviral Treatments**

Practice Point 1: Consider molnupiravir to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 5 to 7 days of the onset of symptoms and at high risk for progressing to severe disease.

Evidence showed benefits of molnupiravir, which may reduce all-cause mortality and COVID-19-specific mortality in patients for whom treatment is initiated within 5 to 7 days of symptom onset (low certainty) compared with placebo. However, evidence showed that there is probably no difference in recovery (moderate certainty) and that there may be no difference in time to recovery or hospital admissions due to COVID-19 (low certainty). Evidence for harms showed that there may be no difference in the incidence of serious adverse events (low certainty) and that there is probably no difference in the incidence of adverse events (moderate certainty) for molnupiravir compared with placebo. The Omicron B.1.1.529 variant is expected to be susceptible to molnupiravir on the basis of currently available information (42).

Practice Point 2: Consider nirmatrelvir-ritonavir combination therapy to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 5 days of the onset of symptoms and at high risk for progressing to severe disease.
**Figure 1. Evidence summary for treatment of confirmed COVID-19 in outpatient settings.**

**Outpatient Treatments of Confirmed COVID-19**

**Population:**
Adults in the Outpatient Setting

**Eligible Studies:**
26 Randomized Trials

**Comparison:**
Placebo

Total Sample Size = 21,212
Sample Size Range: 18 to 5607

Study risk of bias:
9 low, 16 moderate, and 1 high

### Evidence Supports Use
in Patients at High Risk for Progressing to Severe Disease

| Treatment vs. Placebo Trials; Sample Size* | All-Cause Mortality | COVID-19 Mortality | Time to Recovery | Hospital Admission | Serious Adverse Events | Adverse Events |
|------------------------------------------|---------------------|--------------------|------------------|--------------------|-----------------------|---------------|
| **Antivirals**                            |                     |                    |                  |                    |                       |               |
| Molnupiravir                              | May reduce           | May reduce         | Probably no difference | May be no difference | May be no difference | May be no difference |
| 2 RCTs; n = 1637                          | ○○                  | ○○                 | ↔                 | ↔○○                | ↔○○                  | ↔○○           |
| Nirmatrelvir–ritonavir                    | Probably reduces     | No evidence        | No evidence       | Probably reduces   | Very uncertain        | No difference |
| 1 RCT; n = 2246                           | ○○                  | ○○                 | ↓                 | ○○○                | ○○○                  | ○○○           |
| Remdesivir                                | Very uncertain ?     | No evidence        | No evidence       | May improve        | Very uncertain        | No difference |
| 1 RCT; n = 584                            | ○○○                 | ○○                 | ↑                 | ●○○                | ○○○                  | ○○○           |

**Note.** Before initiating COVID-19 treatment, individuals should meet all drug approval criteria.

**Evidence Does Not Support Use**

Casirivimab–Imdevimab | Regdanvimab | Sotrovimab

Do not use monoclonal antibodies to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting unless it is considered effective against a SARS-CoV-2 variant or subvariant locally in circulation. No studies were identified for bebtelovimab.

Azithromycin | Chloroquine/Hydroxychloroquine | Ciclesonide | Convalescent Plasma | Fluvoxamine |
| Ivermectin | Lopinavir–Ritonavir | Nitazoxanide |

* Total baseline sample sizes are reported. Analytic sample sizes might vary by outcome. CoE = certainty of evidence; RCT = randomized controlled trial.
Evidence showed benefits of nirmatrelvir–ritonavir combination therapy, which probably reduces all-cause mortality and hospital admissions due to COVID-19 in patients for whom treatment is initiated within 5 days of symptom onset (moderate certainty) compared with placebo. Evidence for harms showed no difference in the incidence of adverse events (high certainty) between nirmatrelvir–ritonavir combination therapy and placebo. Evidence was very uncertain or lacking for other critical outcomes. The Omicron B.1.1.529 variant and its BA.2 subvariant are expected to be susceptible to nirmatrelvir–ritonavir combination therapy on the basis of currently available information (43). Rebound of COVID-19 has been reported to occur with the use of nirmatrelvir–ritonavir combination therapy between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive result on a viral test after having tested negative (44).

Practice Point 3: Consider remdesivir to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 7 days of the onset of symptoms and at high risk for progressing to severe disease.

Evidence showed benefits of remdesivir, which may improve recovery and reduce hospital admissions due to COVID-19 in patients for whom treatment is initiated within 7 days of symptom onset (low certainty) compared with placebo. Evidence for harms showed that remdesivir probably does not differ from placebo in the incidence of adverse events (moderate certainty). Evidence was very uncertain or lacking for other critical outcomes. The Omicron variant and its subvariants are expected to be susceptible to remdesivir on the basis of currently available information (45). The use of remdesivir requires administration by intravenous infusion in a specialized setting (that is, an infusion center).

TREATMENTS NOT SUPPORTED

Antibiotics

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

Evidence showed no benefit of azithromycin, which may not differ from placebo in recovery (low certainty). Evidence for harms showed that azithromycin may increase the incidence of adverse events (low certainty) compared with placebo. Evidence was very uncertain or lacking for other critical outcomes.

Antiparasitic Treatments

Practice Point 5: Do not use chloroquine or hydroxychloroquine to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

Evidence showed no benefit of hydroxychloroquine. Compared with placebo, hydroxychloroquine may reduce the chance that patients will recover, but there may be no difference in time to recovery or hospital admissions due to...
COVID-19 (low certainty). Evidence for harms showed that hydroxychloroquine may not differ from placebo in the incidence of serious adverse events or adverse events (low certainty). Evidence was very uncertain for other critical outcomes.

Evidence about the efficacy of chloroquine was lacking for all critical outcomes.

**Practice Point 6:** Do not use ivermectin to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

Evidence showed no benefit of ivermectin because there is probably no difference in recovery (moderate certainty) and there may be no difference in mortality or hospital admissions due to COVID-19 (low certainty) compared with placebo. Evidence for harms showed that ivermectin probably does not differ from placebo in the incidence of adverse events (moderate certainty). Evidence was very uncertain for other critical outcomes.

**Practice Point 7:** Do not use nitazoxanide to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

Evidence showed no benefit of nitazoxanide because there is probably no difference in recovery or time to recovery (moderate certainty) and there may be no difference in hospital admissions due to COVID-19 (low certainty) compared with placebo. Evidence for harms showed that there may be no difference in the incidence of serious adverse events (low certainty) and that there is probably no difference in the incidence of adverse events (moderate certainty) for nitazoxanide compared with placebo.

**Practice Point 8:** Do not use lopinavir-ritonavir combination therapy to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

Evidence showed no benefit of lopinavir-ritonavir combination therapy, which may not differ from placebo in hospital admissions due to COVID-19 (low certainty). Evidence for harms showed that there may be no difference in the incidence of serious adverse events and that there may be an increase in adverse events (low certainty) for lopinavir-ritonavir combination therapy compared with placebo. Evidence was very uncertain or lacking for other critical outcomes.

**Monoclonal Antibodies**

**Practice Point 9:** Do not use casirivimab-imdevimab combination therapy to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting unless it is considered effective against a SARS-CoV-2 variant or subvariant locally in circulation.

Evidence showed benefit of casirivimab-imdevimab combination therapy, which reduces time to recovery (high certainty) and probably reduces hospital admissions due to COVID-19 (moderate certainty) compared with placebo. Evidence was very uncertain or lacking for other critical outcomes, including serious adverse events and adverse events. Monoclonal antibodies target the spike protein of the virus. Hence, despite the benefits of casirivimab-imdevimab combination therapy, the efficacy of using monoclonal antibody treatment of COVID-19 varies depending on the SARS-CoV-2 variant. The Omicron variant and its subvariants have markedly reduced susceptibility to casirivimab-imdevimab combination therapy (46). Therefore, this therapy should not be used unless different SARS-CoV-2 variants or subvariants locally in circulation are considered susceptible to it. If casirivimab-imdevimab combination therapy is used, it should be used within 7 days of the onset of symptoms and only in patients who are at high risk for progressing to severe disease.

**Practice Point 10:** Do not use regdanvimab to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting unless it is considered effective against a SARS-CoV-2 variant or subvariant locally in circulation.

Evidence showed benefit of regdanvimab, which probably improves recovery (moderate certainty) compared with placebo. However, regdanvimab may not differ from placebo in time to recovery or hospital admissions due to COVID-19 (low certainty). Evidence for harms showed that there may be no difference in the incidence of adverse events for regdanvimab (low certainty) compared with placebo. Evidence was very uncertain or lacking for other critical outcomes. Monoclonal antibodies target the spike protein of the virus. Hence, despite the benefits of regdanvimab therapy, the efficacy of using monoclonal antibody treatment of COVID-19 varies depending on the SARS-CoV-2 variant. The susceptibility of the Omicron variant and its subvariants to regdanvimab is uncertain. Therefore, this therapy should not be used unless different SARS-CoV-2 variants or subvariants locally in circulation are considered susceptible to it. If regdanvimab therapy is used, it should be used within 7 days of the onset of symptoms and only in patients who are at high risk for progressing to severe disease.

**Table 2. Dosages for Treatment Options**

| Antiviral | Dosage |
|-----------|--------|
| Molnupravir (39) | 800 mg (four 200-mg capsules) taken orally every 12 hours for 5 days |
| Nirmatrelvir-ritonavir combination (40) | 300 mg nirmatrelvir (two 150-mg tablets) with 100 mg ritonavir (one 100mg tablet), with all three tablets taken together twice daily for 5 days |
| Remdesivir (41) | Single loading dose of 200 mg on day 1 followed by once-daily maintenance doses of 100 mg from day 2 via intravenous infusion |

- eGFR = estimated glomerular filtration rate.
- *Based on information available as of 5 October 2022.
onset of symptoms and only in patients who are at high risk for progressing to severe disease.

**Practice Point 11:** Do not use sotrovimab to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting unless it is considered effective against a SARS-CoV-2 variant or subvariant locally in circulation.

Evidence showed benefit of sotrovimab, which may reduce hospital admissions due to COVID-19 (low certainty) compared with placebo. Evidence for harms showed that sotrovimab probably does not differ from placebo in the incidence of adverse events (moderate certainty). Evidence was very uncertain or lacking for other critical outcomes. Monoclonal antibodies target the spike protein of the virus. Hence, despite the benefits of sotrovimab therapy, the efficacy of using monoclonal antibody treatment of COVID-19 varies depending on the SARS-CoV-2 variant. The Omicron BA.2, BA.4, and BA.5 subvariants have markedly reduced susceptibility to sotrovimab therapy (46). Therefore, sotrovimab should not be used unless different SARS-CoV-2 variants or subvariants locally in circulation are considered susceptible to it. If sotrovimab therapy is used, it should be used within 7 days of the onset of symptoms and only in patients who are at high risk for progressing to severe disease.

**Other Treatments**

**Practice Point 12:** Do not use convalescent plasma to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

Evidence showed no benefit of convalescent plasma, which may not differ from placebo in all-cause mortality, time to recovery, or hospital admissions due to COVID-19 (low certainty). Evidence for harms showed that there may be no difference in the incidence of serious adverse events (low certainty) for convalescent plasma compared with placebo. Evidence was very uncertain or lacking for other critical outcomes.

**Practice Point 13:** Do not use ciclesonide to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

Evidence showed no benefit of inhaled or intranasal ciclesonide, which may not differ from placebo in recovery (low certainty). Evidence for harms showed that there may be no difference in the incidence of serious adverse events or adverse events (low certainty) for ciclesonide compared with placebo. Evidence was very uncertain or lacking for other critical outcomes.

**Practice Point 14:** Do not use fluvoxamine to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting.

Evidence showed no benefit of fluvoxamine, which may not differ from placebo in all-cause mortality or hospital admissions due to COVID-19 (low certainty). Evidence for harms showed that there may be no difference in the incidence of adverse events (low certainty) for fluvoxamine compared with placebo. Evidence was very uncertain or lacking for other critical outcomes. One study evaluating the variability in benefits and harms found that fluvoxamine did not differ from placebo in hospital admissions due to COVID-19 based on age, sex, time from symptom onset, or comorbid conditions (19, 31).

**Clinical Considerations**

- These practice points do not provide clinical advice on the comparative effectiveness of the reviewed treatments.
- The decision to initiate treatment of 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), and patient preferences.
- Evidence on outpatient treatment of mild to moderate COVID-19 is rapidly changing as SARS-CoV-2 variants continue to emerge.
- Risk stratification is an important step in the initial evaluation to decide the best approach to COVID-19 treatment in the outpatient setting. The current definition of risk factors for progression to severe COVID-19 can be accessed on the website of the Centers for Disease Control and Prevention (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html).
- Do not use the suggested treatments in asymptomatic patients with confirmed COVID-19.
- Before initiating outpatient treatments of COVID-19, patients should meet all treatment approval criteria, including careful consideration of potential drug interactions.
- The use of remdesivir requires administration by intravenous infusion in a specialized setting (that is, an infusion center).
- Rebound of COVID-19 has been reported to occur with the use of nirmatrelvir-ritonavir combination therapy between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive result on a viral test after having tested negative (44).

**Evidence Gaps**

More research evaluating the efficacy of pharmacologic and biologic treatments of COVID-19 in the outpatient setting is needed, particularly as new variants emerge for which less is known about susceptibility to new and existing treatments.

No placebo-controlled randomized studies evaluated the efficacy of bebtelovimab in the outpatient setting. Recovery and COVID-19-specific mortality were evaluated less frequently than other critical outcomes.

Studies applying prespecified subgroup analyses are needed to assess whether the efficacy of treatments of COVID-19 used in the outpatient setting varies by patient characteristics (age, gender, 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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**CLINICAL GUIDELINE**

ACP Practice Points on Outpatient Treatment of Confirmed COVID-19

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**CLINICAL CONSIDERATIONS**

- These practice points do not provide clinical advice on the comparative effectiveness of the reviewed treatments.
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- Evidence on outpatient treatment of mild to moderate COVID-19 is rapidly changing as SARS-CoV-2 variants continue to emerge.
- Risk stratification is an important step in the initial evaluation to decide the best approach to COVID-19 treatment in the outpatient setting. The current definition of risk factors for progression to severe COVID-19 can be accessed on the website of the Centers for Disease Control and Prevention (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html).
- Do not use the suggested treatments in asymptomatic patients with confirmed COVID-19.
- Before initiating outpatient treatments of COVID-19, patients should meet all treatment approval criteria, including careful consideration of potential drug interactions.
- The use of remdesivir requires administration by intravenous infusion in a specialized setting (that is, an infusion center).
- Rebound of COVID-19 has been reported to occur with the use of nirmatrelvir-ritonavir combination therapy between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive result on a viral test after having tested negative (44).

**EVIDENCE GAPS**

More research evaluating the efficacy of pharmacologic and biologic treatments of COVID-19 in the outpatient setting is needed, particularly as new variants emerge for which less is known about susceptibility to new and existing treatments.

No placebo-controlled randomized studies evaluated the efficacy of bebtelovimab in the outpatient setting. Recovery and COVID-19-specific mortality were evaluated less frequently than other critical outcomes.

Studies applying prespecified subgroup analyses are needed to assess whether the efficacy of treatments of COVID-19 used in the outpatient setting varies by patient characteristics (age, gender, 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.

From American College of Physicians, Philadelphia, Pennsylvania (A.Q.); American College of Physicians, Philadelphia, and Villanova University, Villanova, Pennsylvania (J.Y.); Penn Medicine, Philadelphia, Pennsylvania (M.C.M., M.A.F.); University of Connecticut, Mansfield, Connecticut (R.A.); University of Illinois College of Medicine at Urbana-Champaign, Champaign, Illinois (J.A.J.); University of Massachusetts

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**CLINICAL GUIDELINE**

ACP Practice Points on Outpatient Treatment of Confirmed COVID-19

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**CLINICAL CONSIDERATIONS**

- These practice points do not provide clinical advice on the comparative effectiveness of the reviewed treatments.
- The decision to initiate treatment of 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), and patient preferences.
- Evidence on outpatient treatment of mild to moderate COVID-19 is rapidly changing as SARS-CoV-2 variants continue to emerge.
- Risk stratification is an important step in the initial evaluation to decide the best approach to COVID-19 treatment in the outpatient setting. The current definition of risk factors for progression to severe COVID-19 can be accessed on the website of the Centers for Disease Control and Prevention (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html).
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ACP Practice Points on Outpatient Treatment of Confirmed COVID-19

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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Correction: This article was corrected on 18 April 2023 to account for changes to data reported in the related living, rapid review by Sommer et al (31). A correction has been published (doi:10.7326/L23-0098).

Author contributions are available at Annals.org.

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