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CLINICAL GUIDELINE

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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† Author (participated in discussion and voting).

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§ Nonphysician public representative.
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.

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 from published randomized controlled trials on treatments of COVID-19 in the outpatient setting, and both the practice points and the living, rapid review will be periodically updated. Details of the practice points' living process, including signals for updating and retirement, can be found in ACP's methods articles (32, 33).

Living, Rapid Review

These practice points are based on a living, rapid review funded by ACP and done 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 (31). The living, rapid review searched for studies through 4 April 2022. The review included only peer-reviewed, published (preprints were excluded), placebo-controlled trials of an eligible treatment that was given to adults in an outpatient setting. 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

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

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**
Antibiotics							
Azithromycin vs. placebo 1 RCT (*n* = 263)	? Very uncertain (17) ooo	No evidence –	↔ May be no difference (17) ●oo	No evidence –	? Very uncertain (17) ooo	? Very uncertain (17) ooo	↑ May increase (17) ●oo
Antiparasitics							
Hydroxychloroquine‡ vs. placebo 3 RCTs (*n* = 148 to 456)	? Very uncertain (18, 20, 23) ooo	? Very uncertain (18, 23) ooo	↓ May reduce (23) ●oo	↔ May be no difference (23) ●oo	↔ May be no difference (18, 20, 23) ●oo	↔ May be no difference (18, 20, 23) ●oo	↔ May be no difference (20) ●oo
Ivermectin vs. placebo 5 RCTs (*n* = 24 to 1358)	↔ May be no difference (4, 5, 16, 26, 28) ●oo	? Very uncertain (4, 5, 16) ooo	↔ Probably no difference (4, 16) ●●o	? Very uncertain (4, 16, 28) ooo	↔ May be no difference (4, 5, 16, 26, 28) ●oo	? Very uncertain (5, 16, 26, 28) ooo	↔ Probably no difference (5, 16, 26, 28) ●●o
Nitazoxanide vs. placebo 2 RCTs (*n* = 475 to 1092)	? Very uncertain (21, 22) ooo	? Very uncertain (22) ooo	↔ Probably no difference (21) ●●o	↔ Probably no difference (22) ●●o	↔ May be no difference (21, 22) ●oo	↔ May be no difference (21, 22) ●oo	↔ Probably no difference (21, 22) ●●o
Antivirals							
Lopinavir–ritonavir vs. placebo 1 RCT (*n* = 471)	? Very uncertain (20) ooo	No evidence –	No evidence –	No evidence –	↔ May be no difference (20) ●oo	↔ May be no difference (20) ●oo	↑ May increase (20) ●oo
Molnupiravir vs. placebo 2 RCTs (*n* = 204 to 1433)	↓ May reduce (11) ●oo	↓ May reduce (11) ●oo	↔ Probably no difference (11) ●●o	↔ May be no difference (7) ●oo	↔ May be no difference (11) ●oo	↔ May be no difference (7, 11) ●oo	↔ Probably no difference (7, 11) ●●o
Nirmatrelvir–ritonavir vs. placebo 1 RCT (*n* = 2246)	↓ Probably reduces (10) ●●o	No evidence –	No evidence –	No evidence –	↓ Probably reduces (10) ●●o	? Very uncertain (10) ooo	↔ No difference (10) ●●●
Remdesivir vs. placebo 1 RCT (*n* = 584)	? Very uncertain (8) ooo	No evidence –	↑ May improve (8) ●oo	No evidence –	? Very uncertain (8) ooo	? Very uncertain (8) ooo	↔ Probably no difference (8) ●●o
Monoclonal antibodies							
Casirivimab–imdevimab vs. placebo 1 RCT (*n* = 5607)	? Very uncertain (27) ooo	No evidence –	No evidence –	↓ Reduces (27) ●●●	↓ Probably reduces (27) ●●o	? Very uncertain (27) ooo	? Very uncertain (27) ooo
Regdanvimab vs. placebo 2 RCTs (*n* = 18 to 327)	? Very uncertain (24) ooo	No evidence –	↑ Probably improves (24) ●●o	↔ May be no difference (12, 24) ●oo	↔ May be no difference (24) ●oo	? Very uncertain (12, 24) ooo	↔ May be no difference (12, 24) ●oo
Sotrovimab vs. placebo 1 RCT (*n* = 1057)	? Very uncertain (9) ooo	No evidence –	No evidence –	No evidence –	↓ May reduce (9) –	? Very uncertain (9) ooo	↔ Probably no difference (9) ●●o
Other treatments							
Convalescent plasma vs. placebo 4 RCTs (*n* = 160 to 1225)	↔ May be no difference (13, 15, 25, 29) ●oo	? Very uncertain (15, 25) ooo	No evidence –	↔ May be no difference (29) ●oo	? Very uncertain (25, 29) ooo	↔ May be no difference (13, 15, 25, 29) ●oo	? Very uncertain (25, 29) ooo
Ciclesonide vs. placebo 1 RCT (*n* = 215)	? Very uncertain (6) ooo	? Very uncertain (6) ooo	↔ May be no difference (6) ●oo	No evidence –	? Very uncertain (6) ooo	↔ May be no difference (6) ●oo	↔ May be no difference (6) ●oo
			No evidence	No evidence			

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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**
Fluvoxamine vs. placebo 2 RCTs (*n* = 181 to 1497)	↔ May be no difference (14, 19) ●oo	? Very uncertain (14) ooo	–	–	↔ May be no difference (14, 19) ●oo	? Very uncertain (14) ooo	↔ May be no difference (14) ●oo

RCT = randomized controlled trial.
* Total baseline sample sizes are reported. Analytic sample sizes might vary by outcome.
† ? indicates very uncertain about the effect, ↑ effect increase, ↓ effect decrease, and ↔ no difference in effect. Certainty of evidence: ooo = insufficient, any estimate of effect is very uncertain; ●oo; = 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; ●●o = moderate, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; ●●● = high, further research is very unlikely to change our confidence in the estimate of effect (3).
‡ There was no evidence about the efficacy of chloroquine.

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.

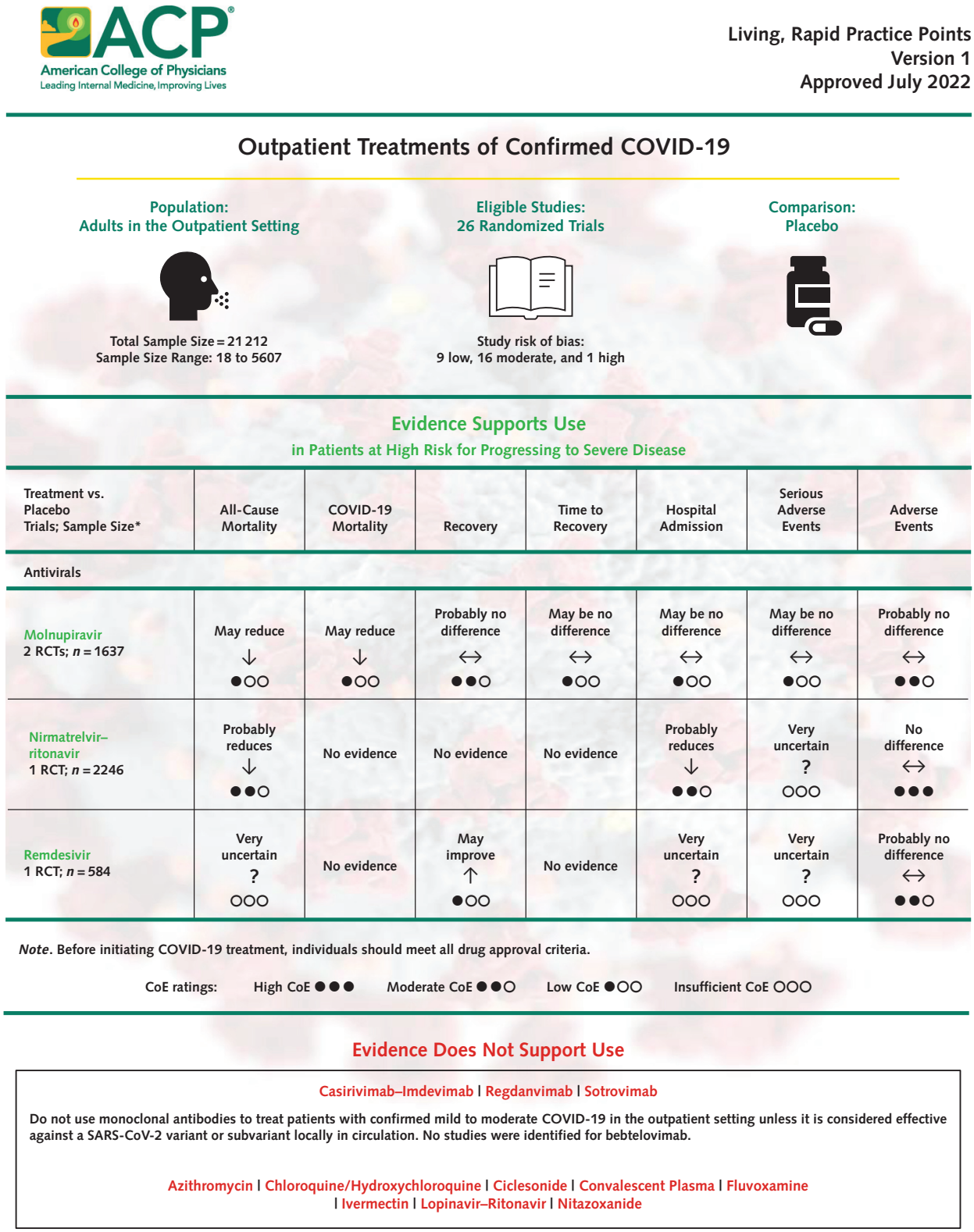
Antiviral Treatments

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).

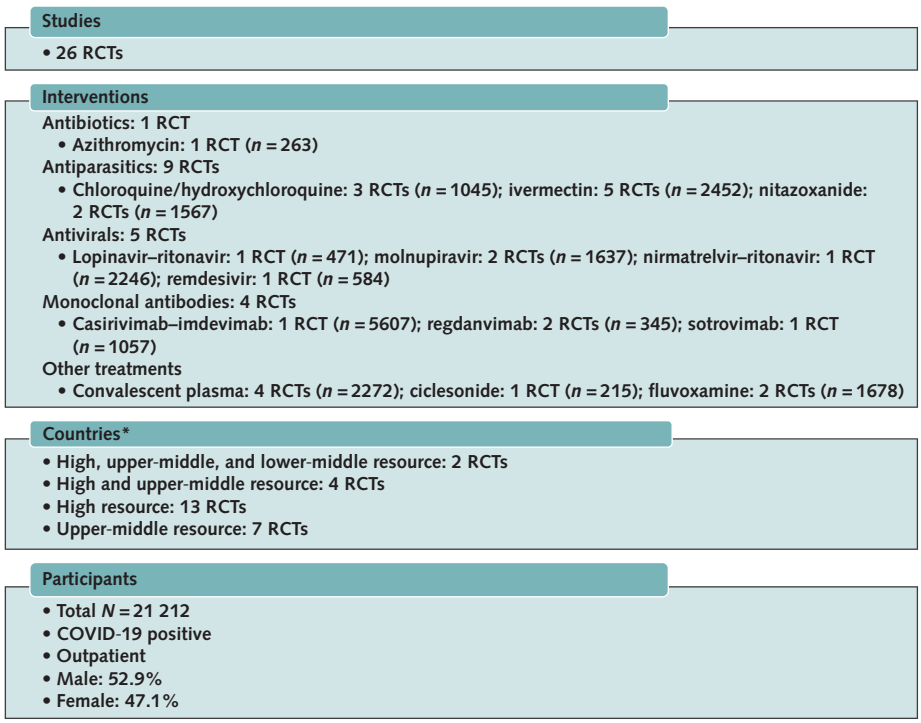
Practice Point 2: Consider nirmatrelvir–ritonavir combination therapy to treat patients with confirmed mild to moderate COVID-19 in the outpatient setting who are within 5 days of the onset of symptoms and at high risk for progressing to severe disease.

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



* Total baseline sample sizes are reported. Analytic sample sizes might vary by outcome. CoE = certainty of evidence; RCT = randomized controlled trial.

Figure 2. Evidence description.



Evidence search and assessment conducted by ACP Center for Evidence Reviews at Cochrane Austria at the University for Continuing Education Krems (Danube University Krems) (31). An updated search for evidence through 4 April 2022 aimed to identify placebo RCTs evaluating selected primary treatment of persons with COVID-19 in the outpatient setting. RCT = randomized controlled trial.
* See reference 30.

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 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

Table 2. Dosages for Treatment Options*

Antiviral	Dosage
Molnupiravir (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 *Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min: 150 mg nirmatrelvir (one 150-mg tablet) with 100 mg ritonavir (one 100mg tablet), with both 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 *For nonhospitalized patients diagnosed with mild to moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, the recommended total treatment duration is 3 days*

eGFR = estimated glomerular filtration rate.
* Based on information available as of 5 October 2022.

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.

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 or time to recovery (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 (28) 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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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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