Annals of Internal Medicine CLINICAL GUIDELINE

Should Remdesivir Be Used for the Treatment of Patients With COVID-19? Rapid, Living Practice Points From the American College of Physicians (Version 2)

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Key Question 1

What are the effectiveness and harms of remdesivir in hospitalized patients with coronavirus disease 2019 (COVID-19)?

Key Question 2

Do effectiveness and harms in hospitalized patients with COVID-19 vary by symptom duration, disease severity, and treatment duration?

Background Update

On 22 October 2020, the U.S. Food and Drug Administration (1) approved the use of remdesivir for treatment of COVID-19 in patients aged 12 years or older and weighing at least 40 kg who require hospitalization. Remdesivir is the first drug to receive federal approval as treatment for COVID-19.

The Scientific Medical Policy Committee (SMPC) of the American College of Physicians (ACP) is maintaining rapid, living practice points on the use of remdesivir as a treatment for COVID-19 (Table 1). This is version 2 of the ACP practice points, which serves to update version 1 that was published on 5 October 2020 (2, 3). This version is based on an updated systematic evidence review done by the U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program in Minneapolis, Minnesota, which has been updated through 7 December 2020 (Appendix, available at Annals.org) (4). The target audience for these practice points includes clinicians, the public, and public health professionals. The target patient population includes all hospitalized, nonpregnant, adult patients with COVID-19. This version was approved by the ACP's Executive Committee of the Board of Regents on behalf of the Board of Regents on 21 December 2020 and submitted to *Annals of Internal Medicine* on 18 December 2020. Updates are currently planned for every 2 months through December 2021.

Overview of New Evidence

The evidence update identified 1 new study (4, 5). The new study evaluated a 10-day course of remdesivir versus standard care and provides new data for all-cause mortality (critical outcome) and new need for ventilation (noninvasive ventilation, invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]) among patients not requiring ventilation at the time of drug initiation (important outcome). The update also reports the final results from 1 study (6) that was included in version 1 as preliminary findings (7) comparing a 10-day course of remdesivir versus placebo for the following outcomes: all-cause mortality, recovery, hospital length of stay, time to recovery, proportion of patients on mechanical ventilation or ECMO, any adverse events, and serious adverse events. Table 2 and the accompanying systematic evidence review summarize changes in the findings (4).

The evidence update did not identify any new evidence comparing a 5-day course of remdesivir versus placebo or standard care or a 5-day course versus a 10-day course.

Updated Practice Points and Rationales (Version 2)

The Figure and Table 2 summarize the updated evidence. Considering the recent U.S. Food and Drug Administration approval for use only in hospitalized

See also:

Related article

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Update Alerts: The authors have specified in the Background Update section and Appendix (available at Annals.org) the interval and stop date for updates to this Practice Points article. As *Annals* receives updates, they will appear in the Comments section of the article on Annals.org. Reader inquiries about updates that are not available at approximately the specified intervals should be submitted as comments to the article.

Table 1. Practice Points (Version 2)

Evidence is emerging about the effectiveness and harms of remdesivir in patients with COVID-19 and whether they vary by symptom duration, disease severity, and treatment duration. The following practice points are based on current best available evidence.

- Practice Point 1: Consider remdesivir* for 5 days to treat hospitalized patients with COVID-19 who do not require mechanical ventilation or ECMO.
- Practice Point 2: Consider extending the use of remdesivir* to 10 days to treat hospitalized patients with COVID-19 who require mechanical ventilation or ECMO within a 5-day course.
- Practice Point 3: Avoid initiating remdesivir to treat hospitalized patients with COVID-19 who are already on mechanical ventilation or ECMO.

What has changed in the practice points since the last version?†

- Practice points shifted away from the previous classifications of "moderate" and "severe" disease to describe disease severity (when data were available) based on respiratory support requirements (e.g., no requirement, supplemental oxygen, or mechanical ventilation/ECMO).
- All practice points now specify the target patient population as "hospitalized" patients.
- Practice Point 3 was added.

COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation.
* Remdesivir is not recommended for patients with an alanine aminotransferase level ≥5 times the upper limit of normal or an estimated glomerular filtration rate <30 mL/min/1.73 m^2 (see further details in Table 3).
† See updated rationales and Table 3 for additional details.

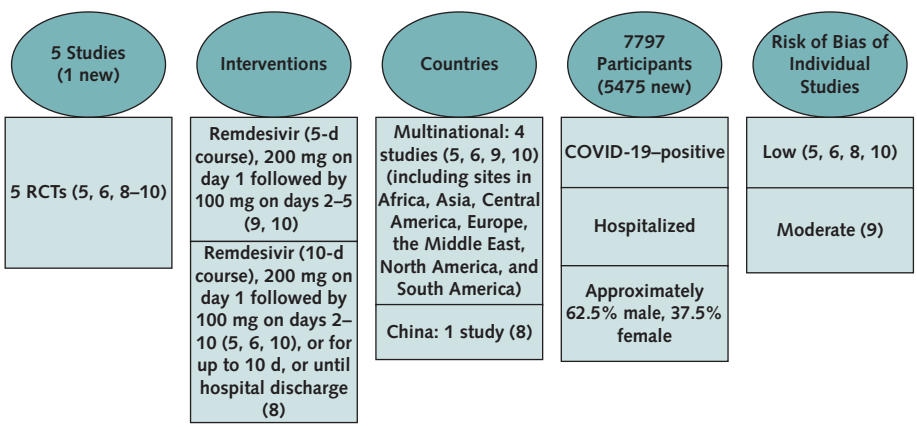
patients, we have modified the practice points to specify the target patient population as *hospitalized*. Table 3 <11, 12> presents clinical considerations. Thresholds applied to determine the magnitude of effect for critical and important outcomes, prespecified by the evidence review team, are provided in Table 4. Table 5 identifies additional evidence gaps. Appendix Table (available at Annals.org) presents the data estimates supporting the practice points.

Practice Point 1: Consider Remdesivir for 5 Days to Treat Hospitalized Patients With COVID-19 Who Do Not Require Mechanical Ventilation or ECMO

Updated Rationale

As in the previous version of the practice points, current evidence suggests an overall net benefit of remdesivir in patients with COVID-19 who do not require invasive mechanical ventilation or ECMO and suggests that 5 days of treatment may be as effective as 10 days, with no increase in potential harms (2). Despite low certainty, the SMPC judged it reasonable to provide clinical advice for the use of a 5-day course of remdesivir in hospitalized patients, particularly considering the limited availability of effective treatments for hospitalized patients with COVID-19. The language of the practice point was changed from "use remdesivir" to "consider remdesivir" to highlight the importance of clinical judgment when making decisions with individual patients about whether to begin remdesivir treatment. Given that disease severity definitions (mild, moderate, severe, and critical) vary widely among the included studies and among different organizations (for example, World Health Organization [WHO], National Institutes of Health, and U.S. Food and Drug Administration) (2), ACP has shifted away from the previous classifications of "moderate" and "severe" in this version. Rather than using these classifications, we use respiratory support requirements as a proxy for disease severity because we expect this to be more clinically useful given the inconsistent definitions. As a result, we have combined the previously separated practice points for patients with moderate COVID-19 and severe COVID-19 who do not require mechanical ventilation or ECMO into a single statement.

Figure. Updated evidence description.



The evidence search and assessment were done by the U.S. Department of Veterans Affairs Evidence Synthesis Program in Minneapolis, Minnesota (4). Updated search for evidence, done through 7 December 2020, aimed to identify RCTs evaluating remdesivir for treatment of COVID-19. COVID-19 = coronavirus disease 2019; RCT = randomized controlled trial.

Table 2. Updated Evidence Summary for the Use of Remdesivir as Treatment for Patients With COVID-19: What Information Does the Evidence Provide?

What has changed in the evidence since the last version?

- 10-day course vs. standard care: added 1 new study (5) providing data for the following outcomes: all-cause mortality and need for mechanical ventilation/ECMO
- 10-day course vs. placebo: updated with final results from 1 study (6) (preliminary results previously reported), providing final results for the following outcomes: all-cause mortality, recovery, hospital length of stay, time to recovery, need for mechanical ventilation/ECMO, any adverse events, and serious adverse events
  - One previously reported outcome (nonserious adverse events) (7) was not reported in the final results and has been removed from this table (6).
- Collapsed placebo and standard care comparisons to a single control comparison
- 10-day course vs. control (placebo or standard care): pooled analyses added for mortality, recovery, clinical improvement, need for mechanical ventilation/ECMO, and serious adverse events
- Shifted away from the previous classifications of "moderate" and "severe" disease to now describe disease severity (when data are available) by oxygen requirements

Outcome	Study Design (Patients, *n*)	Evidence	Certainty of Evidence*
All-cause mortality			
5-d course vs. placebo/ standard care	1 RCT (391)	Remdesivir (5-d course) may slightly reduce mortality compared with standard care (10)	Low
10-d course vs. placebo/ standard care	4 RCTs (7142)	Remdesivir (10-d course) probably does not reduce mortality compared with placebo/standard care (5, 6, 8, 10) *Note: The effect of remdesivir (10-d course vs. placebo/standard care) may vary by baseline respiratory support requirements (5, 6, 8, 10), may not reduce mortality in patients not requiring supplemental oxygen at baseline, may result in a small reduction in mortality in patients requiring supplemental oxygen but not mechanical ventilation at baseline, and may result in a modest increase in mortality in patients requiring mechanical ventilation/ECMO at baseline.†* *Note: The effect of remdesivir (10-d course vs. placebo) may not vary by symptom duration (≤10 vs. >10 d)† (8).*	Moderate
5-d vs. 10-d course	2 RCTs (781)	Remdesivir 5-d course may slightly reduce mortality compared with a 10-d course (9, 10) *Note: The evidence is very uncertain about the effect of remdesivir (5-d course) in patients who progress to requiring mechanical ventilation/ECMO at day 5 (9): A 5-d course may result in a large increase in mortality vs. a 10-d course for patients who progressed to requiring mechanical ventilation/ECMO at day 5, and there may not be a reduction in mortality for patients who were receiving noninvasive positive-pressure ventilation or high- or low-flow oxygen or who were breathing ambient air at day 5 (insufficient certainty of evidence).*	Low
Recovery‡			
5-d course vs. placebo/ standard care	1 RCT (391)	Remdesivir (5-d course) may result in a modest increase in the proportion of patients who recovered compared with standard care (10)	Low
10-d course vs. placebo/ standard care	3 RCTs (1682)	Remdesivir (10-d course) probably results in a modest increase in the proportion of patients who recovered compared with placebo/standard care (6, 8, 10)	Moderate
5-d vs. 10-d course	2 RCTs (781)	Remdesivir 5-d course may result in a modest increase in the proportion of patients who recovered compared with a 10-d course (9, 10)	Low
Hospital length of stay§			
5-d course vs. placebo/ standard care	NA	No evidence	NA
10-d course vs. placebo/ standard care	2 RCTs (1299)	Remdesivir (10-d course) may result in a modest reduction in hospital length of stay compared with placebo (6, 8)	Low
5-d vs. 10-d course	NA	No evidence	NA
Serious adverse events‖			
5-d course vs. placebo/ standard care	1 RCT (391)	Remdesivir (5-d course) may slightly reduce serious adverse events compared with standard care (10)	Low
10-d course vs. placebo/ standard care	3 RCTs (1674)	Remdesivir (10-d course) probably results in a modest reduction in serious adverse events compared with placebo/standard care (6, 8, 10)	Moderate
5-d vs. 10-d course	2 RCTs (781)	Remdesivir 5-d course may result in a modest reduction in serious adverse events compared with a 10-d course (9, 10) *Note: The effect of remdesivir 5-d course compared with a 10-d course may vary by baseline respiratory support requirements† (9, 10): There may be a large reduction in severe adverse events for patients hospitalized with reduced oxygen levels who did not require mechanical ventilation at baseline (9), but there may not be a reduction in severe adverse events in patients without reduced oxygen levels on room air (10).*	Low

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Table 2–Continued

Time to recovery‡			
5-d course vs. placebo/ standard care	1 RCT (391)	Remdesivir (5-d course) may slightly reduce time to recovery compared with standard care (10)	Low
10-d course vs. placebo/ standard care	2 RCTs (1455)	Remdesivir (10-d course) may result in a large reduction in time to recovery compared with placebo (6), but the effect is uncertain for remdesivir (10-d course) compared with standard care (10) *Note: The effect of remdesivir (10-d course) may not vary by symptom duration or baseline respiratory support requirements† (6).*	Low
5-d vs. 10-d course	2 RCTs (781)	Remdesivir 5-d course may slightly reduce time to recovery compared with a 10-d course (9, 10)	Low
Clinical improvement¶			
5-d course vs. placebo/ standard care	1 RCT (391)	Remdesivir (5-d course) may result in a modest increase in clinical improvement compared with standard care (10)	Low
10-d course vs. placebo/ standard care	2 RCTs (629)	Remdesivir (10-d course) may result in a modest increase in clinical improvement compared with placebo/standard care (8, 10)	Low
5-d vs. 10-d course	2 RCTs (781)	Remdesivir (5-d course) may result in a modest increase in clinical improvement compared with a 10-d course (9, 10)	Low
Time to clinical improvement¶			
5-d course vs. placebo/ standard care	NA	No evidence	NA
10-d course vs. placebo/ standard care	1 RCT (237)	Remdesivir (10-d course) may result in a modest reduction in time to clinical improvement compared with placebo (8) *Note: The effect of remdesivir (10-d course) may not vary by symptom duration (≤10 vs. >10 d)†* (8).	Low
5-d vs. 10-d course	NA	No evidence	NA
Invasive mechanical ventilation/ECMO			
5-d course vs. placebo/ standard care	1 RCT (391)	Remdesivir (5-d course) may slightly reduce the proportion of patients on invasive mechanical ventilation/ECMO at follow-up compared with standard care (10)	Low
10-d course vs. placebo/ standard care	4 RCTs (7142)	Remdesivir (10-d course) may slightly reduce the proportion of patients on invasive mechanical ventilation/ECMO at follow-up compared with placebo/ standard care (6, 8, 10) Remdesivir (10-d course) probably does not reduce the proportion of patients with a new need for ventilation (noninvasive, invasive, or ECMO) in those not ventilated at baseline compared with standard care (5)	Low Moderate
5-d vs. 10-d course	2 RCTs (781)	Remdesivir 5-d course may slightly reduce the proportion of patients on invasive mechanical ventilation/ECMO at follow-up compared with a 10-d course (9, 10) *Note: The effect of a 5-d course of remdesivir compared with a 10-d course may vary by baseline respiratory support requirements† (9, 10): There may be a modest reduction in the proportion of patients on mechanical ventilation/ECMO among patients hospitalized with reduced oxygen levels who did not require mechanical ventilation at baseline (9, 10) but there may not be a reduction in the proportion of patients on mechanical ventilation/ECMO among patients without reduced oxygen levels on room air at baseline (9, 10).*	Low

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Table 2–Continued

Any adverse events			
5-d course vs. placebo/ standard care	1 RCT (391)	Remdesivir (5-d course) may slightly increase any adverse events compared with standard care (10)	Low
10-d course vs. placebo/ standard care	3 RCTs (1674)	Remdesivir (10-d course) may not reduce any adverse events compared with placebo/standard care (6, 8, 10)	Low
5-d vs. 10-d course	2 RCTs (781)	Remdesivir 5-d course may modestly reduce any adverse events compared with a 10-d course (9, 10)	Low

COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; NA = not applicable; RCT = randomized controlled trial.
* Insufficient certainty of evidence: confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its effect on a health outcome. Low certainty of evidence: confidence in the effect is limited because the true effect may be substantially different from the estimated effect. Moderate certainty of evidence: confidence in the effect is moderate because the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different. High certainty of evidence: confidence that the true effect is close to the estimated effect.
† The certainty of evidence was not assessed for this comparison determined from a subgroup analysis.
‡ Recovery was defined as discharge from the hospital or hospitalization for infection control purposes only in 1 RCT (6) and as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care in 3 RCTs (8–10).
§ Remdesivir (5-d and 10-d courses) may not decrease the percentage of persons hospitalized between days 11 and 14 (4).
‖ *Severe adverse events* reported in studies included in the evidence review (6, 8–10) were acute coronary syndrome, acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, increased aminotransferase levels, atrial fibrillation, bronchitis, cardiac arrest, cardiopulmonary failure, increased D-dimer level, deep venous thrombosis, diabetic ketoacidosis, dyspnea, endotracheal intubation, decreased glomerular filtration rate, hemorrhage of the lower digestive tract, hypotension, hypoxia, ileus, lung abscess, mechanical ventilation, multiple organ dysfunction syndrome, respiratory distress, respiratory failure, pneumothorax, pulmonary embolism, pulmonary failure, recurrence of COVID-19, septic shock, sepsis, shock, tachycardia, thrombocytopenia, and viral pneumonia. *Any adverse events* reported in the studies included in the evidence review (6, 8–10) were acute kidney injury, acute respiratory failure, increased alanine aminotransferase level, anemia, increased aspartate aminotransferase level, increased blood glucose level, increased blood lipid levels, increased blood urea nitrogen level, constipation, hyperlipidemia, hypoalbuminemia, hypokalemia, hypotension, insomnia, nausea, increased neutrophil count, rash, respiratory failure, increased serum potassium level, reduced serum sodium level, thrombocytopenia, increased total bilirubin level, vomiting, and increased leukocyte count. Any adverse events were not identified in 1 study included in the evidence review (5).
¶ Clinical improvement was defined as a 2-point reduction in patients' admission status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital (whichever came first) in 1 study (8) and as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) in 2 studies (9, 10).

The evidence update did not result in any changes to our previous overall assessment of the balance of benefits and harms. There continues to be a net benefit with both a 5-day and 10-day course compared with placebo or standard care. No new studies were identified reporting on a 5-day course; however, the results for recovery and clinical improvement were updated with longer-term results and show no changes to previous conclusions. Although the inclusion of new data resulted in a finding of little to no effect of a 10-day course on mortality (previously reported as a small reduction) and the new need for ventilation (previously not reported), there

Table 3. Clinical Considerations

- Remdesivir is currently only administered by IV infusion in hospital settings or in a facility that can provide care similar to an acute care hospital setting (1).
- 5-d course in adults is 200 mg IV on day 1 followed by 100 mg/d for a total of 5 d (5 doses).
- 10-d course in adults is 200 mg IV on day 1 followed by 100 mg/d for a total of 10 d (10 doses).
- The practice points do not apply to pregnant women or patients with severe renal or hepatic dysfunction because they were excluded from the studies included in the evidence review.
- NEW: The decision to initiate treatment with remdesivir in hospitalized patients with COVID-19 should be based on clinical judgment; remdesivir should not necessarily be initiated in patients hospitalized for a primary diagnosis unrelated to COVID-19 who have incidentally tested positive for severe acute respiratory syndrome coronavirus 2.
- NEW: For hospitalized patients with COVID-19 whose condition worsens within a 5-d course to require supplemental oxygen but not mechanical ventilation, extending the use of remdesivir should be based on clinical judgment and the balance of benefits and harms, because current evidence is insufficient to determine whether treatment beyond 5 d improves mortality among patients who are receiving noninvasive positive-pressure ventilation or high- or low-flow oxygen or who are breathing ambient air (9).
- The effectiveness of a 10-d course of remdesivir in reducing mortality (5) and time to recovery (6, 7) may not vary by age, sex, or race in hospitalized patients with COVID-19.
- There was not enough information to determine what other treatment interventions, including experimental or off-label medications, were given in the trials.
- Currently, the cost of a 5-d course of remdesivir in the United States varies by insurance status, from $2340 (Indian Health Service and the VA) to $3120 ($520/vial) (U.S. insurers, including Medicare and Medicaid). The cost for those without insurance is currently $390/vial (2, 11).
- The FDA recommends that clinicians assess kidney and hepatic function at baseline and during treatment (5, 12). The FDA recommends the following:
  - Not using remdesivir in patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2.
  - Discontinuing the use of remdesivir if alanine aminotransferase levels increase to >10 times the upper limit of normal or if alanine aminotransferase elevation is accompanied by signs or symptoms of liver inflammation.
- The FDA reports that hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and after administration of remdesivir (5). Additional adverse events include metabolic (hyperglycemia), hepatic (increased serum alanine aminotransferase and aspartate aminotransferase levels), and renal (renal toxicity) events (5, 12).

COVID-19 = coronavirus disease 2019; FDA = U.S. Food and Drug Administration; IV = intravenous; VA = U.S. Department of Veterans Affairs.

Table 4. Thresholds for Determining Magnitude of Effect*

Outcome	Little/No Effect	Small Effect†	Modest Effect‡	Large Effect§
Critical outcomes				
All-cause mortality, %	<1	1 to 2.9	3 to 4.9	≥5
Recovery, %	<2	2 to 4.9	5 to 9.9	≥10
Length of stay, *d*	<1	≥1 to 2	>2 to <3	≥3
Severe adverse event, %	<1	1 to 4.9	5 to 9.9	≥10
Important outcomes				
Time to recovery, *d*	<1	≥1 to 2	>2 to <3	≥3
Clinical improvement, %	<2	2 to 4.9	5 to 9.9	≥10
Time to clinical improvement, *d*	<1	≥1 to 2	>2 to <3	≥3
Mechanical ventilation or ECMO, %	<1	1 to 4.9	5 to 9.9	≥10
Any adverse event, %	<2	2 to 4.9	5 to 19.9	≥20

ECMO = extracorporeal membrane oxygenation.
* Measured as absolute risk difference (when not otherwise specified).
† Described as "slight increase or decrease."
‡ Described as "modest increase or decrease."
§ Described as "large increase or decrease."

remains a reported benefit for recovery (modest increase), clinical improvement (modest increase), and length of stay (modest reduction), along with fewer serious adverse events (modest difference) among those treated. Further, patient compliance data from the final report of 1 study comparing a 10-day course versus placebo continue to show that a 10-day course (10 doses) was used in fewer than half of the patients receiving remdesivir (41.2%), and an even lower percentage of patients (38.1%) received fewer than 10 doses because they recovered and were discharged from the hospital (2, 3, 6). Finally, there are no new studies directly comparing a 5-day versus a 10-day course.

An important area of uncertainty relates to the use of remdesivir in patients who do not require supplemental oxygen at hospitalization, although we expect that most patients with a diagnosis of COVID-19 are admitted with respiratory signs and symptoms. A newly reported pooled subgroup analysis comparing a 10-day course versus placebo or standard care showed that there may be a small reduction in mortality among patients requiring supplemental oxygen (but not mechanical ventilation) at the time of drug initiation, but that there may be little to no difference in mortality in patients not requiring supplemental oxygen at the time of drug initiation (5, 6, 8). In consideration of limited treatment options for COVID-19, the SMPC considered the evidence as insufficient to advise against considering the use of remdesivir in patients who do not require supplemental oxygen at the time of drug initiation. Further research is needed on treatment effects by oxygenation status at baseline.

Hence, our past conclusions are unchanged; in patients not requiring invasive mechanical ventilation or ECMO at the time of drug initiation, a 5-day course of remdesivir may be superior to a 10-day course for the following outcomes, with no evidence of increased harm with the shorter duration: mortality (slight reduction), recovery (modest increase), time to recovery (slight reduction), clinical improvement (modest increase), and the proportion of patients on invasive mechanical ventilation or ECMO at follow-up (slight reduction).

Practice Point 2: Consider Extending the Use of Remdesivir to 10 Days to Treat Hospitalized Patients With COVID-19 Who Require Mechanical Ventilation or ECMO Within a 5-Day Course

Updated Rationale

The previous version of the practice points concluded that evidence suggests a reduction in mortality with extension of remdesivir treatment to 10 days that outweighs potential harms among patients with COVID-19 who progress to requiring mechanical ventilation or ECMO by day 5 (2). This conclusion was based on evidence suggesting a net benefit for a 10-day course of remdesivir in these patients compared with placebo or standard care and on a post hoc analysis considering

Table 5. Evidence Gaps

- Additional studies are needed to assess the optimal treatment duration with remdesivir (i.e., 5-d vs. 10-d course) and to determine if there is variation in the optimal duration of treatment with remdesivir across different subgroups of patients.
- Additional studies are needed to assess if the effectiveness of remdesivir treatment for COVID-19 varies by severity (e.g., respiratory support requirements) of COVID-19.
- There is a need for studies assessing whether remdesivir treatment outcomes vary by symptom duration in patients with COVID-19.
- NEW: Studies are needed to determine the effectiveness of extending an initial 5-d course of remdesivir to 10 d and to identify subpopulations of patients with COVID-19 who may benefit from longer treatment.
- Future studies should consider evaluating additional critical and important clinical outcomes, such as respiratory failure or duration of mechanical ventilation.

COVID-19 = coronavirus disease 2019.

variation in disease severity (respiratory support requirements) when comparing a 5-day course with a 10-day course of remdesivir (9). The post hoc analysis found that treatment beyond 5 days did not improve mortality among patients who were receiving noninvasive positive-pressure ventilation or high- or low-flow oxygen or who were breathing ambient air; however, among patients with COVID-19 who progressed to requiring mechanical ventilation or ECMO at day 5, continued treatment through 10 days resulted in lower mortality (9).

The updated evidence report now rates the post hoc analysis (previously not rated) as insufficient, but the direction of effect still suggests potential benefit (based on this post hoc analysis and the overall findings for a 10-day course versus placebo or standard care). The SMPC also considered that currently, with limited availability of other effective treatments to manage hospitalized patients with COVID-19, extending treatment to 10 days is a consideration, particularly for patients who have not demonstrated any adverse effect profile while receiving the 5-day course.

Practice Point 3: Avoid Initiating Remdesivir to Treat Hospitalized Patients With COVID-19 Who Are Already on Mechanical Ventilation or ECMO

New Rationale

Our current understanding of COVID-19 progression is that patients who are admitted on mechanical ventilation or ECMO have likely progressed beyond the viral stage of the illness to the inflammatory stage and are less likely to improve from antivirals; hence, it is important to avoid any additional toxicity from remdesivir, unless there is evidence for potential benefit. This understanding is consistent with findings from a newly reported pooled subgroup analysis of 3 studies comparing a 10-day course of remdesivir versus placebo or standard care, which showed that remdesivir may result in a modest increase in mortality in patients receiving mechanical ventilation or ECMO at the time of drug initiation (5, 6, 8). This is also consistent with previously reported post hoc findings from 1 study that showed no improvement in time to recovery with a 10-day course among patients receiving invasive mechanical ventilation or ECMO at baseline (6). Studies evaluating the effectiveness of a 5-day course have not investigated the effect of baseline COVID-19 severity.

Although the evidence base is limited, the SMPC considers these findings a signal that the potential harms of remdesivir may outweigh the potential benefits in patients who are receiving invasive mechanical ventilation or ECMO at baseline and cautions against initiating remdesivir treatment in these patients.

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Note: The practice points are developed by the SMPC of the ACP. The practice points are guides only and may not apply to all patients and all clinical situations. 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 5 March 2021 to correct the description of the magnitude of the mortality reduction with remdesivir for patients receiving supplemental oxygen but not needing ventilation and to clarify in the Appendix Table that certainty of evidence was not assessed for the subgroup analyses reported for several outcomes.

Current author addresses and author contributions are available at Annals.org.

Ann Intern Med. doi:10.7326/M20-8101

References

1. **U.S. Food and Drug Administration.** FDA approves first treatment for COVID-19. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19 on 3 November 2020.

2. **Wilt TJ, Kaka AS, MacDonald R, et al.** Rapid Response: COVID-19: Remdesivir for Hospitalized Adults. Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs; 2020. VA ESP Project 09-009.

3. **Wilt TJ, Kaka AS, MacDonald R, et al.** Remdesivir for adults with COVID-19. A living systematic review for an American College of Physicians Practice Points. Ann Intern Med. 5 October 2020. [Epub ahead of print].. doi:10.7326/M20-5752

4. **Kaka AS, MacDonald R, Greer N, et al.** Major update: remdesivir for adults with COVID-19. A living systematic review and meta-analysis for the American College of Physicians Practice Points. Ann Intern Med. 9 February 2021. [Epub ahead of print]. doi:10.7326/M20-8148

5. **WHO Solidarity Trial Consortium.** Repurposed antiviral drugs for COVID-19—interim WHO Solidarity trial results. N Engl J Med. 2 December 2020. [Epub ahead of print]. doi:10.1056/NEJMoa2023184
6. **Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members.** Remdesivir for the treatment of Covid-19—final report. N Engl J Med. 2020;383:1813-1826. [PMID: 32445440] doi:10.1056/NEJMoa2007764
7. **Beigel JH, Tomashek KM, Dodd LE.** Remdesivir for the treatment of Covid-19—preliminary report. Reply [Letter]. N Engl J Med. 2020;383:994. [PMID: 32649078] doi:10.1056/NEJMc2022236
8. **Wang Y, Zhang D, Du G, et al.** Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569-1578. [PMID: 32423584] doi:10.1016/S0140-6736(20)31022-9
9. **Goldman JD, Lye DCB, Hui DS, et al; GS-US-540-5773 Investigators.** Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020;383:1827-1837. [PMID: 32459919] doi:10.1056/NEJMoa2015301
10. **Spinner CD, Gottlieb RL, Criner GJ, et al; GS-US-540-5774 Investigators.** Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 2020;324:1048-1057. [PMID: 32821939] doi:10.1001/jama.2020.16349
11. **O'Day D.** An open letter from Daniel O'Day, Chairman & CEO, Gilead Sciences. Stories @Gilead. 29 June 2020. Accessed at https://stories.gilead.com/articles/an-open-letter-from-daniel-oday-june-29 on 7 December 2020.
12. **Lexicomp.** Remdesivir: drug information. Accessed at www.uptodate.com/contents/remdesivir-united-states-investigational-agent-refer-to-prescribing-and-access-restrictions-drug-information on 18 June 2020.

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Appendix: Overview of Practice Points Development Process and Methods

Practice Points Development Process

The SMPC, in collaboration with staff from ACP's Department of Clinical Policy, developed these practice points on the basis of a rapid and living systematic evidence review done by the VA Evidence Synthesis Program in Minneapolis, Minnesota (2). The SMPC comprises 11 internal medicine physicians representing various clinical areas of expertise and 1 public (nonclinician) member and includes members with expertise in epidemiology, evidence synthesis, healthy policy, and guideline development. In addition to contributing clinical, scientific, and methodological expertise, Clinical Policy staff provided administrative support and liaised among the SMPC, the evidence review funding entity and evidence team, and the journal. Clinical Policy staff and the SMPC reviewed and prioritized potential topic suggestions from ACP members, SMPC members, and ACP governance. A committee subgroup, including the SMPC chair, worked with staff to draft the key questions and led the development of the practice points. Clinical Policy staff worked with the subgroup and an independent evidence review team to refine the key questions and determine appropriate evidence synthesis methods for each key question. Via conference calls and e-mail, Clinical Policy staff worked with the committee subgroup to draft the practice points on the basis of the results of the rapid and living systematic evidence review. The full SMPC reviewed and approved the final practice points. Before journal submission, ACP's Executive Committee of the Board of Regents also reviewed and approved the practice points on behalf of the ACP Board of Regents. The evidence review team will continually update the evidence review. ACP will update the practice points based on the evidence review using the same process as the first version described above. Updates are currently planned for every 2 months through December 2021. The SMPC will continuously assess the priority of the topic and the overall state of evidence, including the anticipated rate of new evidence, and may choose to modify the update intervals accordingly (any modifications will be described in an Update Alert).

Methodological Differences From the WHO Guideline

On 20 November 2020, the WHO published an update of its "Therapeutics and COVID-19: Living Guideline" (13). In this guideline, the WHO "suggests against administering remdesivir in addition to standard care, in hospitalized patients with COVID-19, regardless of disease severity" (conditional recommendation). A review of current, publicly available documents (13–15) showed that there are 3 important methodological differences between the WHO guideline and the ACP practice points that may contribute to differing conclusions between ACP and WHO.

- The WHO guideline is based on a network meta-analysis comparing multiple drug treatments. The ACP practice points were developed on the basis of a VA Evidence Synthesis Program living systematic evidence review with the sole focus of evaluating the benefits and harms of remdesivir in hospitalized patients (4).
- The WHO guideline considered the effect of remdesivir regardless of its duration of use, whereas the ACP practice points focused specifically on the effectiveness and comparative effectiveness of differing durations of remdesivir use—5 days and 10 days compared with placebo or standard care or the other duration.
- The WHO guideline did not make a recommendation based on disease severity. WHO requested subgroup analyses from its network meta-analysis team and judged the credibility to be insufficient when assessing the variation in effectiveness of remdesivir by disease severity (WHO severity classifications). ACP provides clinical advice based on disease severity (baseline oxygen requirements). ACP considered subgroup analyses reported within the individual studies and those done de novo by the authors of the supporting rapid, living systematic review (4).

Appendix Table. Updated Estimates: Use of Remdesivir as Treatment for Patients With COVID-19*

Outcome	Study Design (Patients, *n*)	Evidence	Certainty of Evidence†
All-cause mortality			
5-d course vs. placebo/ standard care (FU: 11 d)	1 RCT (391)	Remdesivir 5-d course, 0% (0/191), vs. standard care, 2% (4/200); ARD, −2.0% (95% CI, −4.2% to 0.2%) (10)	Low
10-d course vs. placebo/ standard care (FU: 11–29 d)	4 RCTs (7142)	Remdesivir 10-d course, 10.6% (384/3635), vs. placebo/standard care, 11.2% (394/3507); pooled ARD, −0.8% (CI, −2.2% to 0.7%) (5, 6, 8, 10) *Note: The effect of remdesivir (10-d course vs. placebo/standard care) by baseline respiratory support requirements¶:* • *In patients not requiring supplemental oxygen: remdesivir 10-d course, 17.2% (16/929), vs. placebo/standard care, 21.6% (20/927); pooled ARD, −0.5% (CI, −0.2% to 0.8%) (5, 6, 10)* • ***In patients receiving supplemental oxygen who did not need ventilation (mechanical ventilation/ECMO): remdesivir 10-d course, 9.7% (212/2189), vs. placebo/standard care, 12.1% (251/2082); pooled ARD, −2.3% (CI, −4.2% to −0.4%) (5, 6, 8)*** • *In patients receiving ventilation (mechanical ventilation/ECMO): remdesivir 10-d course, 30.6% (156/509), vs. placebo/standard care, 24.8% (123/495); pooled ARD, 4.9% (CI, −0.6% to 10.3%) (5, 6)* *Note: The effect of remdesivir (10-d course vs. placebo) by symptom duration¶ (8):* • *≤10 d of symptoms: remdesivir, 11% (8/71), vs. placebo, 15% (7/47); ARD, −3.6% (CI, −16.2% to 8.9%)* • *>10 d of symptoms: remdesivir, 14% (12/84), vs. placebo, 10%; ARD, 4.6% (CI, −8.2% to 17.4%)*	Moderate
5-d vs. 10-d course (FU: 11–14 d)	2 RCTs (781)	5-d course, 8.0% (16/200), vs. 10-d course, 10.7% (21/197); ARD, −2.7% (CI, −8.4% to 3.1%) (9) 5-d course, 0% (0/191), vs. 10-d course, 1.0% (2/193); ARD, −1.0% (CI, −2.8% to 0.7%) (10) *Note: Among patients receiving mechanical ventilation/ECMO at day 5 (9):* • *Remdesivir 5-d course, 40% (10/25), vs. remdesivir 10-d course, 17% (7/41); ARD, 23.0% (CI, 0.5% to 4.5%) (insufficient certainty of evidence)* • *Note: Among patients who were receiving noninvasive positive-pressure ventilation or high- or low-flow oxygen or who were breathing ambient air at 5 d, treatment beyond 5 d did not reduce mortality.*	Low
Recovery‡			
5-d course vs. placebo/ standard care (FU: 28 d)	1 RCT (391)	**Proportion of patients recovered with remdesivir 5-d course, 91.6% (175/191), vs. standard care, 85% (170/200); ARD, 6.6% (CI, 0.3% to 12.9%) (10)**	**Low**
10-d course vs. placebo/ standard care (FU: 28–29 d)	3 RCTs (1682)	**Proportion of patients recovered with remdesivir 10-d course, 77.3% (683/884), vs. placebo/standard care, 71.6% (571/798); pooled ARD, 6.5% (CI, 2.4% to 10.7%) (6, 8, 10)**	Moderate
5-d vs. 10-d course (FU: 11–14 d)	2 RCTs (781)	Proportion of patients recovered with remdesivir 5-d course, 64.5% (129/200), vs. 10-d course, 53.8% (106/197); baseline-adjusted ARD, 6.3% (CI, −2.8% to 15.4%) (9) Proportion of patients recovered with remdesivir 5-d course, 73.8% (141/191), vs. 10-d course, 68.4% (132/193); ARD, 5.4% (CI, −3.6% to 14.5%) (10)	Low
Hospital length of stay§			
5-d course vs. placebo/ standard care	NA	No evidence	NA
10-d course vs. placebo/ standard care (FU: 28–29 d)	2 RCTs (1299)	10-d course, median 12 d (IQR, 6 to 28 d), vs. placebo, median 17 d (IQR, 8 to 28 d); MD, −5 d (CI, −7.7 to −2.3 d) (6, 8) Remdesivir 10-d course, median 25 d (IQR, 16 to 38 d), vs. placebo, median 24 d (IQR, 18 to 36 d); MD, 0 d (IQR, −4.0 to 4.0 d) (6, 8)	Low
5-d vs. 10-d course	NA	No evidence	NA
Serious adverse events‖			
5-d course vs. placebo/ standard care (FU: 11 d)	1 RCT (391)	Remdesivir 5-d course, 4.7% (9/191), vs. standard care, 9.0% (18/200); ARD, −4.3% (CI, −9.3% to 0.7%) (10)	Low
10-d course vs. placebo/ standard care (FU: 11–29 d)	3 RCTs (1674)	**Remdesivir 10-d course, 19.2% (169/880), vs. placebo/standard care, 25.3% (201/794); pooled ARD, −6.3% (CI, −10.2% to −2.4%) (6, 8, 10)**	Moderate
5-d vs. 10-d course (FU: 11–14 d)	2 RCTs (781)	**Remdesivir 5-d course, 21.0% (42/200), vs. 10-d course, 34.5% (68/197); ARD, −13.5% (CI, −22.2% to −4.8%) (9)** Remdesivir 5-d course, 4.7% (9/191), vs. 10-d course, 5.2% (10/193); ARD, −0.5% (CI, −4.8% to 3.9%) (10)	Low

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Appendix Table–Continued

Outcome	Study Design (Patients, *n*)	Evidence	Certainty of Evidence†
		Note: The effect of remdesivir 5-d course vs. 10-d course by baseline respiratory support, among patients with radiologic evidence of pneumonia¶: • *In patients with reduced oxygen levels who did not require mechanical ventilation at study entry, there was a large reduction in severe adverse events with a 5-d course vs. a 10-d course (13.5%) (9).* • *In patients without reduced oxygen levels on room air at study entry, there was little to no difference in severe adverse events (0.5% decrease) between a 5-d course vs. a 10-d course (10).*	
Time to recovery‡			
5-d course vs. placebo/standard care (FU: 11 d)	1 RCT (391)	Remdesivir 5-d course, median 6 d (IQR, 5 to 10 d), vs. standard care, median 7 d (IQR, 4 to 15 d); HR, 1.18 (CI, 0.96 to 1.45) (10)	Low
10-d course vs. placebo/standard care (FU: 29 d)	2 RCTs (1455)	Remdesivir 10-d course, median 8 d (IQR, 4 to 13 d), vs. standard care, median 7 d (IQR, 4 to 15 d); HR, 1.11 (CI, 0.90 to 1.37) (10) **Remdesivir 10-d course, median 10 d (IQR, 9 to 11 d), vs. placebo, median 15 d (IQR, 13 to 18 d); *P* < 0.001** **Rate ratio, 1.29 (CI, 1.12 to 1.49) (6, 8)** *Note: The effect of remdesivir (10-d course) by symptom duration¶ (6, 7):* • *≤9 d (median) of symptoms: HR, 1.32 (CI, 1.09 to 1.61)* • *>9 d (median) of symptoms: HR, 1.29 (CI, 1.04 to 1.59)* *Note: The effect of remdesivir (10-d course) by baseline respiratory support requirements¶ (6, 7):* • *Patients receiving mechanical ventilation/ECMO at study entry (HR, 0.98 [CI, 0.70 to 1.36])* • *Patients receiving high-flow oxygen or noninvasive mechanical ventilation at study entry (HR, 1.09 [CI, 0.76 to 1.57])* • *Patients receiving oxygen at study entry (HR, 1.45 [CI, 1.18 to 1.79])* • *Patients not receiving oxygen at study entry (HR, 1.29 [CI, 0.91 to 1.83])*	Insufficient Low
5-d vs. 10-d course (FU: 11–14 d)	2 RCTs (781)	Remdesivir 5-d course, median 10 d (IQR, 6 to 18 d), vs. remdesivir 10-d course, median 11 d (IQR, 7 d to not able to estimate); *P* NS; HR, 0.81 (CI, 0.64 to 1.04) (9) Remdesivir 5-d course, median 6 d (IQR, 5 to 10 d), vs. remdesivir 10-d course, median 8 d (IQR, 4 to 13 d); HR NR (10)	Low
Clinical improvement**			
5-d course vs. placebo/standard care (FU: 28 d)	1 RCT (391)	Remdesivir 5-d course, 89.5% (171/191), vs. standard care, 83% (166/200); ARD, 6.5% (CI, −0.3% to 13.3%) (10)	Low
10-d course vs. placebo/standard care (FU: 28 d)	2 RCTs (629)	Remdesivir 10-d course, 65.2% (103/158), vs. placebo, 57.7% (45/78); ARD, 7.5% (CI, −5.7% to 20.7%) (8) **Remdesivir 10-d course, 90.2% (174/193), vs. standard care, 83% (166/200); ARD, 7.2% (CI, 0.5% to 13.8%) (10)**	Low
5-d vs. 10-d course (FU: 11–14 d)	2 RCTs (781)	Remdesivir 5-d course, 64.5% (129/200), vs. remdesivir 10-d course, 54.3% (107/197); baseline-adjusted ARD, 6.5% (CI, −2.8% to 15.7%) (9) Remdesivir 5-d course, 70.2% (134/191), vs. remdesivir 10-d course, 65.3% (126/193); ARD, 4.9% (CI, −4.5% to 14.2%) (10)	Low
Time to clinical improvement**			
5-d course vs. placebo/standard care	NA	No evidence	NA
10-d course vs. placebo/standard care (FU: 28 d)	1 RCT (237)	Remdesivir 5-d course, median 21 d (IQR, 13 to 28 d), vs. placebo, median 23 d (IQR, 18 to 36 d); HR, 1.23 (CI, 0.87 to 1.75) (6, 8) *Note: The effect of remdesivir (10-d course) by symptom duration¶ (8):* • *≤10 d of symptoms: remdesivir, median 18 d (IQR, 12 to 28 d), vs. placebo, median 23 d (IQR, 15 to 28 d); HR, 1.52 (CI, 0.95 to 2.43)* • *>10 d of symptoms: remdesivir 23 d vs. placebo 24 d; HR, 1.07 (CI, 0.63 to 1.83)*	Low
5-d vs. 10-d course	NA	No evidence	NA
Invasive mechanical ventilation/ECMO			
5-d course vs. placebo/standard care (FU: 11 d)	1 RCT (391)	Remdesivir 5-d course, 0% (0/191), vs. standard care, 2.0% (4/200); ARD, −2.0% (CI, −4.2% to 0.2%) (10)	Low
10-d course vs. placebo/standard care (FU: 11–29 d)	4 RCTs (1299)	Remdesivir 10-d course, 11.3% (100/887), vs. placebo/standard care, 16.5% (132/799); pooled ARD, −4.8% (CI, −8.0% to −1.5%) (5, 6, 8, 10) Remdesivir 10-d course, 11.9% (295/2489), vs. placebo/standard care, 11.5% (284/2475); ARD, 0.4% (CI, −1.4% to 2.2%) (5)	Low Moderate

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Appendix Table–Continued

Outcome	Study Design (Patients, *n*)	Evidence	Certainty of Evidence†
5-d vs. 10-d course (FU: 11–14 d)	2 RCTs (781)	**Remdesivir 5-d course, 8.0% (16/200), vs. remdesivir 10-d course, 16.8% (33/197); ARD, −8.8% (CI, −15.2% to −2.3%) (9)** Remdesivir 5-d course, 0% (0/191), vs. remdesivir 10-d course, 0.5% (1/193); ARD, −0.5% (CI, −1.9% to 0.9%) (10) *Note: The effect of remdesivir 5-d course vs. 10-d course by baseline oxygen requirements among patients with radiologic evidence of pneumonia who did not require mechanical ventilation at study entry¶:* • In patients with reduced oxygen levels not requiring mechanical ventilation at study entry, there was a modest reduction in the proportion of patients on mechanical ventilation/ECMO at follow-up with a 5-d course vs. a 10-d course (8.8%) (9). • In patients without reduced oxygen levels on room air at study entry, there was little to no difference in the proportion of patients on mechanical ventilation/ECMO at follow-up between a 5-d course vs. a 10-d course (0.5% reduction) (10).	Low
Any adverse events			
5-d course vs. placebo/standard care (FU: 11 d)	1 RCT (391)	Remdesivir 5-d course, 51.3% (98/191), vs. standard care, 47.0% (93/200); ARD, 4.8% (CI, −5.1% to 14.7%) (10)	Low
10-d course vs. placebo/standard care (FU: 11–29 d)	3 RCTs (1674)	10-d course, 59.1% (520/880), vs. placebo/standard care, 58.7% (466/794); pooled ARD, −0.3% (CI, −5.0% to 4.4%) (6, 8, 10)	Low
5-d vs. 10-d course (FU: 11–14 d)	2 RCTs (781)	Remdesivir 5-d course, 70.5% (141/200), vs. remdesivir 10-d course, 73.6% (145/197); ARD, −3.1% (CI, −11.9% to 5.7%) (9) Remdesivir 5-d course, 51.3% (98/191), vs. remdesivir 10-d course, 58.5% (113/193); ARD, −7.2% (CI, −17.2% to 2.7%) (10)	Low

ARD = absolute risk difference; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; FU = follow-up; HR = hazard ratio; IQR = interquartile range; MD = mean difference; NA = not applicable; RCT = randomized controlled trial; RR = relative risk.

* Statistically significant findings are in boldface.

† Insufficient certainty of evidence: confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its effect on a health outcome. Low certainty of evidence: confidence in the effect is limited because the true effect may be substantially different from the estimated effect. Moderate certainty of evidence: confidence in the effect is moderate because the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different. High certainty of evidence: confidence that the true effect is close to the estimated effect.

‡ Recovery was defined as discharge from the hospital or hospitalization for infection control purposes only in 1 RCT (6) and as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care in 3 RCTs (8-10).

§ Remdesivir (5-d course and 10-d course) may not decrease the percentage of persons hospitalized between days 11 and 14 (4).

‖ *Severe adverse events* reported in studies included in the evidence review (6, 8–10) were acute coronary syndrome, acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, increased aminotransferase levels, atrial fibrillation, bronchitis, cardiac arrest, cardiopulmonary failure, increased D-dimer level, deep venous thrombosis, diabetic ketoacidosis, dyspnea, endotracheal intubation, decreased glomerular filtration rate, hemorrhage of the lower digestive tract, hypotension, hypoxia, ileus, lung abscess, mechanical ventilation, multiple organ dysfunction syndrome, respiratory distress, respiratory failure, pneumothorax, pulmonary embolism, pulmonary failure, recurrence of COVID-19, septic shock, sepsis, shock, tachycardia, thrombocytopenia, and viral pneumonia. *Any adverse events* reported in studies included in the evidence review (6, 8–10) were acute kidney injury, acute respiratory failure, increased alanine aminotransferase level, anemia, increased aspartate aminotransferase level, increased blood glucose level, increased blood lipid levels, increased blood urea nitrogen level, constipation, hyperlipidemia, hypoalbuminemia, hypokalemia, hypotension, insomnia, nausea, increased neutrophil count, rash, respiratory failure, increased serum potassium level, reduced serum sodium level, thrombocytopenia, increased total bilirubin level, vomiting, and increased leukocyte count. Any adverse events were not identified in 1 study included in the evidence review (5).

¶ The certainty of evidence was not assessed for this comparison determined from a subgroup analysis.

** Clinical improvement was defined as a 2-point reduction in patients' admission status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital (whichever came first) in 1 study (8) and as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) in 2 studies (9, 10).

Web References

13. **World Health Organization.** Therapeutics and COVID-19: living guideline. Accessed at www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline on 7 December 2020.

14. Siemieniuk R, Rochwerg B, Agoritsas T, et al. A living WHO guideline on drugs for Covid-[WEB_ONLY]19. BMJ. 2020;370: m3379. [PMID: 32887691] doi:10.1136/bmj.m3379

15. **World Health Organization.** Summary: what is this living guideline? Accessed at https://app.magicapp.org/#/guideline/nBkO1E on 7 December 2020.