

UPDATE ALERTS

Should Remdesivir Be Used for the Treatment of Patients With COVID-19? Rapid, Living Practice Points From the American College of Physicians (Version 2, Update Alert 3)

This is an update of the American College of Physicians' living, rapid practice points on the use of remdesivir for treatment of COVID-19 (1-3). This update is based on an updated living, rapid systematic review that included studies published through 19 October 2021 (4) and identified 2 new studies meeting inclusion criteria. One was a primary randomized controlled trial (5); the second was a substudy (6) of a primary randomized controlled trial (7) that was already included in version 2 of the practice points and systematic review (1-3, 8-10) but assesses new data on outcomes of interest not evaluated by the primary study (7). Both new studies evaluated a 10-day course of remdesivir versus standard care. In addition, this update includes data on serious adverse events and any adverse events from 1 substudy (11) not reported in the previous evidence review (10). No new evidence has been identified assessing a 5-day course of remdesivir compared with placebo or standard care or compared with a 10-day course. The **Supplement** (available at [Annals.org](https://annals.org)) summarizes the key questions and practice point development process and provides an updated evidence overview and summary of findings, clinical considerations, and evidence gaps.

PRACTICE POINTS

The following practice points are based on the best available evidence about the effectiveness and harms of remdesivir and its variability by symptom duration, disease severity, and treatment duration in patients with COVID-19. The target patient population includes all hospitalized, nonpregnant, adult patients with COVID-19. Although treatment with remdesivir in outpatient settings is an important area of research, these practice points do not address it.

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

The evidence update did not result in any changes to our previous overall assessment, as there continues to be an overall net benefit of remdesivir with both a 5-day course (1, 2, 8, 9) and a 10-day course (1, 3, 4, 8, 10) as well as evidence suggesting that 5 days of treatment may be as effective as 10 days (1, 8).

None of the new studies evaluated a 5-day course of remdesivir. Assessing the updated evidence evaluating a 10-day course of remdesivir compared with placebo or standard care (4-6, 11), we still judged there to be an overall net benefit (low- to moderate-certainty evidence) for a 10-day course across all outcomes: recovery (modest increase), hospital length of stay (modest reduction), clinical improvement (modest increase), time to recovery (large reduction), time to clinical improvement (slight reduction), need for invasive ventilation or extracorporeal membrane oxygenation (ECMO) at follow-up (slight reduction), and serious adverse events (slight reduction; previously a modest reduction), with no differences in mortality or new need for mechanical ventilation or ECMO

and a slight increase in any adverse events (previously little to no difference).

The new studies did not evaluate a 5-day course compared with a 10-day course. Thus, our previous conclusion remains unchanged that a 5-day course compared with a 10-day course (1, 8) may reduce mortality (slightly), time to recovery (slightly), and need for invasive ventilation or ECMO at follow-up (slightly) and may increase recovery (modestly) and clinical improvement (modestly) with fewer serious adverse events and fewer of any adverse events (both modestly). In addition, previously reported patient compliance data from 1 study further support clinical advice for considering use of a 5-day course; of patients allocated to receive a 10-day course versus placebo, fewer than half (41.2%) received all 10 doses, with an even lower percentage (38.1%) receiving all 10 doses because they recovered and were discharged from the hospital (12, 13).

Previous evidence comparing a 10-day course of remdesivir with placebo or standard care showed a modest reduction in mortality among patients requiring supplemental oxygen (but not invasive ventilation) and little to no difference in mortality in patients not requiring supplemental oxygen at the time a 10-day course was initiated (1, 8). Considering the expectation that most patients with a diagnosis of COVID-19 are admitted with respiratory signs and symptoms, we determined that the evidence is insufficient to advise against considering use of remdesivir in patients who do not require supplemental oxygen at the time of drug initiation.

Practice Point 2: Consider Extending the Use of Remdesivir to 10 Days to Treat Hospitalized Patients With COVID-19 Who Develop the Need for Invasive Ventilation or ECMO Within a 5-Day Course**Updated Rationale**

Our previous conclusion remains unchanged: Evidence suggests an overall net benefit with a 10-day course of remdesivir (1, 3, 4, 8, 10) and a reduction in mortality with extension of remdesivir treatment to 10 days in hospitalized patients with COVID-19 who progress to requiring ventilation or ECMO by day 5 of remdesivir therapy, both of which outweigh potential harms (8, 14).

The updated findings (4-6, 11) show an overall net benefit (low- to moderate-certainty evidence) for a 10-day course across all outcomes: recovery (modest increase), hospital length of stay (modest reduction), clinical improvement (modest increase), time to recovery (large reduction), time to clinical improvement (slight reduction), need for invasive ventilation or ECMO at follow-up (slight reduction), and serious adverse events (slight reduction), with no differences in mortality or new need for invasive ventilation or ECMO and a slight increase in any adverse events. In addition, a previously reported post hoc analysis assessing variation in disease severity (respiratory support requirements) between a 5-day course and a 10-day course suggested that continued treatment through 10 days resulted in lower mortality among patients who progressed to requiring invasive ventilation or ECMO at day 5. However, no improvement was observed in mortality among patients who were receiving noninvasive positive-pressure ventilation, were receiving high- or low-flow oxygen, or were breathing ambient air (8, 14).

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

The update did not identify any relevant studies for practice point 3; thus, our previous conclusion remains unchanged. Previous evidence from a pooled subgroup analysis in the systematic review found that patients receiving invasive ventilation or ECMO at the time of drug initiation may have a modest increase in mortality (8), and a post hoc finding in one study showed no improvement in time to recovery among patients receiving invasive ventilation or ECMO at baseline (12, 13) with a 10-day course versus placebo or standard care. These findings are consistent with our current understanding of COVID-19 progression that patients who are admitted on invasive ventilation or ECMO have likely progressed beyond the viral stage of the illness to the inflammatory stage and are less likely to improve with antivirals; hence, it is important to avoid any additional toxicity from remdesivir, in the absence of demonstrated benefit and given possible harms.

RETIREMENT FROM LIVING STATUS

The Scientific Medical Policy Committee has decided to retire this topic from living status in order to balance current priorities with existing resources (15), considering that surveillance was originally planned through December 2021 and the last 3 updates did not result in important changes to conclusions.

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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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