Remdesivir for Treatment of COVID-19 Disease

A Rapid Guidance Summary from the

Penn Medicine Center for Evidence-based Practice

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This Rapid Guidance Summary is a description of existing guidance and evidence reviews from a variety of sources that was in effect at the time of publication. It should not be used or interpreted as a clinical practice guideline, but instead can be used in development of local recommendations and policies.

Key questions answered in this summary

- Is remdesivir a safe and effective treatment for COVID-19 disease?
- Which patients is remdesivir appropriate to use in?

Use of remdesivir for prevention of disease is outside the scope of this report.

Summary of major recommendations

- NIH now makes a moderate-level recommendation for use of remdesivir in hospitalized patients with severe COVID-19 disease.
- FDA has granted Emergency Use Authorization for remdiesivir, is controlling distribution of the drug, and supply of drug from the manufacturer is unclear.
- Interim clinical trial evidence suggests remdesivir may lead to faster recovery, but trials are still underway.
- Evidence on the safety of remdesivir for COVID-19 treatment is lacking.

Public health agency and professional society guidelines on remdesivir

Source	Recommendations
NIH May 12	On the basis of preliminary clinical trial data the Panel recommends the investigational antiviral agent remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease (defined as having SpO2 94% on ambient air [at sea level], requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]) (moderate recommendation based on evidence from cohort or non-randomized studies). Remdesivir is not approved by the Food and Drug Administration (FDA); however, it is available through an FDA emergency use authorization (EUA) for the treatment of hospitalized adults and children with COVID-19 and is currently being investigated in clinical trials. Remdesivir is also available through an emergency access program for children (<18 years of age) and pregnant patients. Additional data on the use of remdesivir for patients with COVID-19, including analyses of important patient subgroups, are expected soon and may further inform the Panel's recommendation. The Panel does not recommend remdesivir for the treatment of mild or moderate COVID-19 outside of a clinical trial (strong recommendation based on expert opinion).
Ontario May 11	Remdesivir is not recommended for patients with COVID-19 outside of approved clinical trials. Remdesivir is currently unavailable in Canada.
FDA May 1	On May 1, 2020, FDA issued an EUA to allow remdesivir to be distributed and used by licensed health care providers to treat adults and children hospitalized with severe COVID-19. Severe COVID-19 is defined as patients with an oxygen saturation (SpO2) 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO), a heart-lung bypass machine.

Evidence reviews on remdesivir

Reviewer	Findings
ASHP May 15	See Appendix for detailed findings. Most promising direct-acting antiviral currently being investigated for COVID-19 Various clinical trials initiated in US, China, and other countries. Optimal dosage and duration of treatment not known. Not commercially available. Safety and efficacy of remdesivir for treatment of COVID-19 is not established; additional data needed.
CADTH May 15	See linked document for full rapid systematic review. Conclusions: Three RCTs, Wang et al. and ACTT, which were stopped early, and GS-US-540-5773, which is ongoing, provide the information to date regarding the efficacy and safety of remdesivir. Wang et al. did not find remdesivir to be more effective than placebo for any outcome but the study was potentially underpowered to detect a difference between groups due to a smaller sample size than planned and a smaller than anticipated treatment effect with remdesivir. ACTT results are not published in full but showed a reduced time to recovery with remdesivir. Mortality, however, was not statistically significantly different than for those treated with placebo. The limited trial results available are conflicting and methodological issues make the results of Wang et al. difficult to interpret. Publication of additional trial results are required to confirm the efficacy of remdesivir in adult patients with severe COVID-19. Further, without access to full trial details and outcome data, the current evidence is insufficient to determine which patients are more likely to benefit from remdesivir and if a shorter course (five days) of remdesivir offers the same benefits as a longer course of treatment. Additional trial results are required to determine the potential place in therapy of remdesivir. As such, this report will be updated as new information becomes available.
ACP May 15	Remdesivir (RDV,GS-5734) is a prodrug of an adenosine analog with potent activity against RNA virus families through targeting the viral RNA dependent RNA polymerase. As of May 1, 2020 the FDA issued emergency use authorization for remdesivir as a treatment for hospitalized patients severely ill with Covid-19. Authorization was primarily based on unpublished results of the Adaptive Covid-19 Treatment Trial. See FDA Fact Sheet f or dosing, monitoring, and reporting instructions. NIH/NIADD Adaptive COVID-19 Treatment Trial (ACTT) This double-blind, placebo-controlled trial enrolled nearly 1,100 patients with laboratory-confirmed SARS-CoV-2 infection and severe lung disease requiring hospitalization. 68 sites joined the study, 47 in the USA plus 21 in Europe and Asia. Patients in the treatment group received 200 mg remdesivir IV on day 1 (enrollment) followed by 100 mg each day for the duration of hospitalization, for up to 10 days total. Study enrollment ended April 19, and interim analysis data was reported on April 29, prior to formal peer review, but after review by the study's international oversight board. The interim data has been reported to demonstrate clinical benefit of remdesevir: Time to recovery: patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p<0.001$); median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Survival: benefit was suggested but did not meet statistical significance in the interim analysis, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p=0.059$). Dose analysis: lay press interviews of study supervisors have reported that 5 days of infusion were as beneficial as 10 days of infusion, but that data has not yet been peer reviewed. Other remdesevir trials: possible efficacy for selected patients In addition to awaiting final, peer-reviewed results of the ACTT, remdesevir continues to be assessed in other trials. Trials have been equivocal without significant benefit documented, although some data suggests possible benefit in selected settings: A randomized, double-blind, placebo-controlled, multi-center trial in China enrolled hospitalized patients with laboratory-confirmed Covid-19 pneumonia; patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. Remdesivir was not associated with statistically significant improvement in time to clinical improvement, but there was a nonsignificant reduction in time to clinical improvement for those patients treated within the first 10 days of symptom onset time the trial was prematurely discontinued with insufficient enrollment (240 Chinese adults enrolled instead of the targeted 450); interpretation of the (underpowered) data is pending peer review, but there was no detected difference in time to clinical improvement (median: 21 days for remdesevir and 23 days for placebo). An open label, manufacturer-supported, observational series of 53 compassionate use cases was restricted to hospitalized patients who had creatinine clearance >30 ml/min and serum ALT & AST < 5 x upper limit of normal. Limitations of the series include the lack of correction for baseline variables, lack of a direct comparison group, some missing follow up data, and variable duration of treatment. The study revealed no unexpected adverse effects and suggested a possible clinical benefit. For information on other clinical trials of remdesivir, access clinicaltrials.gov.

Penn Medicine May 15	In SARS-CoV-2, evidence is from a single case report among one patient and an in vitro study. Several trials are currently underway investigating in vivo use in SARS-CoV-2. Limitations of evidence: • Inadequate evidence in SARS-CoV-2. • Inadequate in vivo evidence in MERS & SARS-CoV-1. • A clinical trial investigating remdesivir in Ebola was discontinued early after demonstrating a decreased mortality benefit relative to other investigational drugs. • Limited evidence in pregnancy.
Southern Cal. May 15	Preliminary results from an NIH randomized control study of 1063 patients showed a median time to recovery of 11 days with remdesivir vs. 15 days with placebo (P<0.001). Gilead also announced results from their own Phase 3 trial evaluating 5-day vs 10-day dosing duration, which suggested that 5 days of treatment may be as effective as 10 days. Based on these findings, the FDA issued emergency use authorization. for the drug to be used for severe, hospitalized patients. Gilead donated supplies to treat approximately 100,000-200,000 patients to the federal government. The U.S. government will prioritize regions and hospitals to receive the donated medication. Despite the encouraging news, these two promising studies are preliminary and have not yet been peer-reviewed. Many are calling for the release of the full data-set. Additionally, not all the news for remdesivir has been favorable. Another placebo controlled trial in the Lancet failed to demonstrate benefit.
Hopkins May 13	Remains investigational and is not FDA-approved. FDA issued an emergency use authorization on May 1, distribution federally controlled—unclear how much supply available. The drug has been used in the US under compassionate use; now limited only to pregnancy and children < 18. Preliminary results of an NIH-sponsored clinical trial (ACTT; NCT04280705) for COVID-19 patients with evidence of lung involvement: Median time to recovery reduced by 31% (11d v 15d). Mortality trend suggested (8% v 11.6%), but not statistically significant. The data safety monitoring board did not suggest halting the study because of a clear and convincing benefit of treatment. NIH has suggested that this drug will be standard for comparison in adaptive clinical research trials. Another RCT, from China, did not show benefit. Additional trials in progress.
NIH May 12	Preliminary data from a multi-national, randomized, placebo-controlled trial (Adaptive COVID-19 Treatment Trial [ACTT]) of hospitalized patients with COVID-19 showed that patients who were randomized to receive remdesivir had a shorter time to clinical recovery than those who received placebo. There is not enough clinical trial data to assess the role of remdesivir for patients with mild to moderate COVID-19.
EM-RAP May 11	There is limited availability through compassionate use. Two recently published studies suggest that remdesivir may speed recovery, especially if given within 10 days of symptom onset. In an NIH-sponsored placebo-controlled study, preliminary data noted a more rapid recovery in the treatment group (11 vs. 15 days). There was a trend toward a mortality benefit, 8% versus 11.6%. A Chinese placebo-controlled study of 237 patients noted no significant difference between treated and untreated patients but a trend toward faster recovery in the treatment group.
Washington May 9	Remdesivir is a potent inhibitor of SARS-CoV-2 RNA-dependent RNA polymerase that is active in vitro; results of compassionate use of remdesivir reported in a case series of 63 patients: clinical improvement observed in 68%, and 57% of intubated patients were able to be extubated, but no control group or viral load measurement, and adverse events seen in 60% (including elevated LFTs); a double-blind placebo-controlled RCT in China found no benefit from remdesivir, although there was a trend toward more rapid clinical improvement in patients with symptoms 10d.

CEBM May 6	Short-term outcomes have been reported for 53 of 61 patients with COVID-19 treated in over 20 different hospitals on three continents, as part of a compassionate-use (so-called “expanded access”) programme organized by the manufacturer, and not as part of a clinical trial). Thirty were being ventilated and four treated with extracorporeal membrane oxygenation (ECMO) at the start of remdesivir treatment. After a median of 18 days, 25 /53 patients (47%) had been discharged from hospital and 7/53 (13%) had died. Mortality was 5% among patients who were not ventilated. The overall probability of improvement by 18 days was 68% (95% confidence interval 40–80%). Sixty percent (32/53) of patients had one or more adverse event, which were serious in 23% (12/53). The most common adverse events were abnormal liver function, diarrhoea, rashes, renal impairment, and hypotension. As the authors stated, “Interpretation of the results of this study is limited by the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on eight of the patients initially treated, and the lack of a randomized control group.” Now the results of a Chinese double-blind randomized multicentre trial of remdesivir at ten hospitals in Hubei Province in patients with severe COVID-19 have been published, after publication of a protocol on February 6 (NCT04257656). In 237 patients, 158 of whom were given IV remdesivir 200 mg on day 1 and 100 mg/day thereafter for 10 days and 79 of whom were given placebo there was no statistically significant change in the time to clinical improvement: median 21 (IQR 13-28) versus 23 (IQR 15-28) days. There was no difference in the rate of adverse events (66% versus 64% of patients); remdesivir was withdrawn early because of adverse events in 18 patients (12%) versus four patients (5%) in whom placebo was withdrawn early (not statistically significant). Although an effect on viral load would have been expected, in view of the mechanism of action of remdesivir, that was not seen. This trial, whose authors originally planned to enroll 453 patients, was termi- nated early on April 15 because of lack of subjects when the epidemic came under control in Hubei Province. On February 5 the same investigators logged a protocol for another similar trial, intending to enroll 308 patients with mild or moderate disease (NCT04252664); this trial was suspended on 15 April and no data have been published. Since then, incomplete and unreviewed data from other studies have been released into the public domain. Most recently (April 30), Anthony Fauci made public some conclusions about a trial being run by the National Institute of Allergy and Infectious Diseases (NIAID), without providing the methods or data on which the conclusions were based, saying that he had an ethical obligation to reveal that remdesivir appeared to shorten recovery times, so that patients currently taking a placebo could have access to it. Since the full results of this trial have not been published, even as a preprint, this is most unusual and unhelpful for physicians trying to make decisions on behalf of their patients. A May 11 “report card” identifies 9 clinical trials in progress. Commentary on quality of the evidence published May 13.

Medical center guidance on remdesivir

Hospital	Recommendation
Penn Medicine May 15	Non-hospitalized patients and hospitalized patients with mild illness and no pneumonia: symptomatic treatment and monitoring are preferred. Hospitalized patients with pneumonia but not criticially ill: consider remdesivir through Emergency Use Authorization if patient eligible and drug is available. Critically ill (non-pregnant): consider remdesivir through Emergency Use Authorization if patient eligible and drug is available. Pregnant patient (hospitalized): consider supportive care and symptomatic treatment, or compassionate use remdesivir. Remdesivir should not be used outside of the acute hospital setting, even in patients that received it as an inpatient and are discharged; patients who are discharged while still within the treatment duration window will be considered to have completed treatment.
Brigham May 12	Mild disease: Not recommended at this time given lack of data and limited supplies of investigational agents. Moderate disease (SpO2 > 94% on room air): Consider remdesivir via open label clinical trial. If not eligible, consider hydroxychloroquine or favipiravir via an RCT. Severe disease: Consider remdesivir via open label clinical trial. If not eligible, consider hydroxychloroquine or favipiravir via an RCT. Can consider remdesivir via emergency use authorization if certain in-house criteria are met and supply is available. Consider tocilizumab, canakinumab, or sarilumab via RCTs. Severe disease with critical illness (respiratory failure, systemic inflammatory response syndrome, multi-organ failure): Consider remdesivir via open label clinical trial. If not eligible, consider hydroxychloroquine via an RCT. Can consider remdesivir via emergency use authorization if certain in-house criteria are met and supply is available. Consider sarilumab via RCTs. If not eligible, consider risks and benefits of use of off-label anti- inflammatory therapies (tocilizumab, anakinra, steroids). Pregnant patients: In severe disease, consider remdesivir via compassionate use. If remdesivir cannot be used, weigh risks and benefits of hydroxychloroquine.
Mass. General May 8	Remdesivir received emergency use authorization from the FDA on May 1, 2020. As of May 8, 2020, the allocation for emergency use is still being determined at MGH. Remdesivir is available via compassionate use for pregnant women and children < 18 years of age. Data regarding remdesivir includes a trial from China with negative results and an announcement by NIH suggesting efficacy in reducing hospital stay and a trend toward mortality benefit. The FDA authorized emergency use on May 1, 2020.

Guidance sources

ACP–American College of Physicians

ASHP–American Society of Health System Pharmacists CADTH–Canadian Agency on Drugs and Technologies in Health CEBM–University of Oxford Centre for Evidence-based Medicine EM-RAP–Emergency Medicine Reviews and Perspectives

NIH–National Institutes of Health COVID-19 Treatment Guidelines Panel Ontario–University Health Network Antimicrobial Stewardship Program (Canada) SIDP–Society of Infectious Diseases Pharmacists

Update history

May 18: Updated NIH guideline recommends use of remdesivir in patients with severe disease (updated guideline and new conclusion). New systematic review from CADTH. New FDA Emergency Use Authorization. Significant update to ASHP evidence review with new appendix added to this report. New evidence reviews from ACP and University of Southern California, other evidence reviews updated. Hospital guidance updated. Deleted hospital guidance more than two weeks old.

April 29: Initial report.

About this report

A Rapid Guidance Summary is a focused synopsis of recommendations from selected guideline issuers and health care systems, intended to provide guidance to Penn Medicine providers and administrators during times when latest guidance is urgently needed. It is not based on a complete systematic review of the evidence. Please see the CEP web site (http://www.uphs.upenn.edu/cep) for further details on the methods for developing these reports.

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Appendix. Summary of ASHP findings

Randomized, double-blind, placebo-controlled trial in hospitalized adults with severe COVID-19 in China (NCT04257656; Wang et al): Pts were randomized 2:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily on days 2-10) or placebo initiated within 12 days of symptom onset. Primary outcome was time to clinical improvement within 28 days after randomization or hospital discharge, whichever came first. ITT population included 158 pts treated with remdesivir and 78 pts treated with placebo; 32% of pts also received interferon -2b, 28% also received LPV/RTV, and 66% also received corticosteroids during hospitalization. Median time to clinical improvement was not significantly different in remdesivir group (21 days) vs placebo group (23 days); 28-day mortality rate was similar in both groups (14 vs 13%). When remdesivir was initiated within 10 days of symptom onset, median time to clinical improvement was numerically shorter (but not statistically significant) compared with placebo group (18 vs 23 days). Duration of invasive mechanical ventilation was numerically shorter (but not statistically significant) in remdesivir group; only a small percentage of pts (0.4%) were on invasive mechanical ventilation at time of enrollment. Remdesivir did not result in significant reduction in SARS-CoV-2 viral load in nasopharyngeal, oropharyngeal, and sputum samples. Remdesivir was discontinued in 18 pts (12%) because of adverse effects.

Note: Enrollment was terminated before the pre-specified number of pts was attained (lack of available pts); trial was insufficiently powered to detect assumed differences in clinical outcome.

Phase 3 randomized, open-label trial in hospitalized adults with severe COVID-19 (NCT04292899) sponsored by the manufacturer (Gilead): Initial study protocol designed to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg once daily for total of 5 or 10 days) in conjunction with standard of care in pts not receiving mechanical ventilation; protocol subsequently modified to add extension arms to evaluate safety and efficacy of 10-day regimen of remdesivir in conjunction with standard of care in pts who are or are not receiving mechanical ventilation.

Manufacturer announced that data available for the initial 397 pts not requiring mechanical ventilation at study entry (200 received a 5-day regimen and 197 received a 10-day regimen) indicate similar clinical improvement with both treatment durations. Time to clinical improvement for 50% of pts was 10 days in the 5-day treatment group vs 11 days in the 10-day treatment group. At day 14, 129/200 pts (64.5%) in the 5-day group and 106/197 pts (53.8%) in the 10-day group achieved clinical recovery. Pts who received remdesivir within 10 days of symptom onset had improved outcomes compared with those treated after more than 10 days of symptoms.

Note: Data regarding this initial pt population (e.g., disease severity and comorbidities at study enrollment, additional supportive treatment received) not provided to date.

Phase 3 randomized, open-label trial in pts with moderate COVID-19 (NCT04292730) sponsored by the manufacturer (Gilead) is evaluating safety and antiviral activity of 5- and 10-day regimens of remdesivir in conjunction with standard of care compared with standard of care alone.

Phase 3 adaptive, randomized, placebo-controlled trial (NCT04280705) in hospitalized adults sponsored by NIAID: Pts received remdesivir (200 mg IV on day 1, then 100 mg once daily for duration of hospitalization up to 10 days total) or placebo. Sponsor announced that preliminary data analysis (total of 1063 pts) indicated shorter median time to recovery in remdesivir group (11 days) vs placebo group (15 days) and suggested that remdesivir treatment may have provided a survival benefit (mortality rate 8% in remdesivir group vs 11.6% in placebo group).

Note: Data regarding the pt population (e.g., disease severity and comorbidities at study enrollment, time to initiation of treatment after symptom onset, additional supportive treatment received) not provided to date.

Expanded access IND protocol (NCT04323761): The manufacturer (Gilead) has established a protocol for emergency access to remdesivir for the treatment of severe acute COVID-19

Compassionate use access: The manufacturer (Gilead) is transitioning from individual compassionate use requests to an expanded access program for emergency access to the drug for severely ill pts with confirmed COVID-19. New individual compasssionate use requests cannot be accepted, with the possible exception of requests for pregnant women and children <18 years of age with confirmed infections and severe manifestations of the disease. https://rdvcu.gilead.com/

Compassionate use access (NCT04302766): May be available for DoD personnel through treatment IND protocol sponsored by US Army Medical Research and Development Command

Data from the manufacturer's compassionate use program: Preliminary data are available for a cohort of 53 adults from multiple sites in the US, Italy, Japan, and other countries who were hospitalized with severe COVID-19 and received treatment with remdesivir; 40 pts received the full 10- day regimen (200 mg IV on day 1, then 100 mg IV on days 2-10), 10 pts received 5-9 days and 3 pts received less than 5 days of treatment with the drug. At baseline, 30 pts (57%) were receiving mechanical ventilation and 4 (18%) were receiving extracorporeal membrane oxygenation (ECMO). Over a median follow-up of 18 days after first dose, 36 pts (68%) showed clinical improvement based on oxygen-support status and 8 pts (15%) worsened. There were 7 deaths (13%), including 6 pts receiving invasive ventilation. Adverse effects (e.g., increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension) were reported in 32 pts (60%); 12 pts (23%) had serious adverse effects (e.g., multiple organ dysfunction syndrome, septic shock, acute kidney injury, hypotension); 4 pts (8%) discontinued the drug because of adverse effects. 16 Note: Data presented for this small cohort of pts offers only limited information regarding efficacy and safety of remdesivir for treatment of COVID-19. There was no control group and, although supportive therapy could be provided at the discretion of the clinician, it is unclear whether pts at any of the various study sites also received other therapeutic agents being used for treatment of COVID-19. In addition, data were not presented regarding the effects of remdesivir on viral load.