Remdesivir

Section last reviewed and updated 2/7/2022

Last literature search conducted 1/31/2022

Recommendation 1 (UPDATED): Among patients (ambulatory or hospitalized) with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests remdesivir initiated within seven days of symptom onset rather than no remdesivir. (Conditional recommendation, Low certainty of evidence)

Remarks:

- Dosing for remdesivir is 200 mg on day one followed by 100 mg on days two and three. Pediatric dosing is 5 mg/kg on day 1 and 2.5 mg/kg on subsequent days.
- Options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, molnupiravir, and neutralizing monoclonal antibodies. Patient specific factors (e.g., patient age, symptom duration, renal function, drug interactions), product availability, and institutional capacity and infrastructure should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.

Recommendation 2: In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence)

Recommendation 3a: In hospitalized patients with severe* COVID-19, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence)

*Severe illness is defined as patients with SpO_2 ≤94% on room air.

Recommendation 3b: In patients with COVID-19 on invasive ventilation and/or ECMO, the IDSA panel suggests against the routine initiation of remdesivir (Conditional recommendation, Very low certainty of evidence)

Why is remdesivir considered for treatment?

Remdesivir (GS-5734) is an antiviral drug with potent *in vitro* activity against a range of RNA viruses including MERS-CoV, SARS-CoV-1 and SARS-CoV-2 [1-3]. Remdesivir acts by causing premature termination of viral RNA transcription [3]. Its use improved disease outcomes and reduced viral loads in SARS-CoV-1 infected mice [2]. In rhesus macaques, therapeutic treatment with remdesivir showed reduction in SARS-CoV-2 loads, pathologic changes, and progression of clinical disease [4]. In this same animal model, remdesivir treatment initiated 12 hours post-inoculation reduced clinical signs, reduced virus replication in the lungs, and decreased the presence and severity of lung lesions.

Similar to other antiviral drugs, from a mechanistic perspective remdesivir is more likely to be beneficial early in the course of the disease when viral burden is high. Though earlier studies were not specifically designed to evaluate the impact of early initiation of remdesivir, subgroup analyses of some RCTs [5, 6] suggested that patients treated earlier in their course of disease with remdesivir (i.e., within 10 days of symptom onset) experienced shorter recovery times.

Summary of the evidence

<u>Patients with mild-to-moderate disease who are at high risk for progression to severe COVID-19</u>

Four RCTs compared treatment with remdesivir or no remdesivir for treatment of ambulatory and hospitalized patients with mild-to-moderate COVID-19; however, only one trial [7] evaluated treatment of high-risk ambulatory patients with mild-to-moderate COVID-19 with remdesivir earlier in the course of their illness (i.e., remdesivir was initiated within 7 days of symptom onset). Given what is now known about the success of early treatment on potential benefit in high-risk patients, data from Gottlieb supported the early initiation of remdesivir in

high risk hospitalized and ambulatory patients with mild-to-moderate disease. Additional details about the identified trials are below.

One RCT compared treatment with three days of intravenous (IV) remdesivir (200 mg on day one followed by 100 mg on days two and three) or no remdesivir in unvaccinated patients [7]. The study enrolled patients at high risk for progression (e.g., obesity, diabetes mellitus, hypertension, immune compromise etc.) or age 60 years or older who were symptomatic seven days or less without prior treatment (e.g., monoclonal antibodies), but were not expected to receive oxygen at time of enrollment (>94% on room air). The outcomes assessed were mortality, hospitalizations for any cause, and COVID-19-related medically as well as serious adverse events.

Three RCTs compared treatment with five days of remdesivir (200 mg day one, 100 mg daily days 2-5), 10 days of remdesivir (200 mg day one, 100 mg daily days 2-10), or no remdesivir for patients hospitalized with oxygen saturation >94% on room air [5, 8, 9]. The outcomes assessed were mortality, clinical improvement, and serious adverse events. These three trials, conducted earlier in the pandemic in hospitalized patients, demonstrated a longer time from symptom onset to remdesivir administration, ranging from a median of 8-9 days. In addition, Adaptive Covid-19 Treatment Trial (ACTT-1) and SOLIDARITY provided subgroup analyses among patients with mild to moderate disease [5, 9]. Randomization and lack of blinding failed to control for or balance receipt of co-interventions (e.g., treatment with dexamethasone, tocilizumab, hydroxychloroquine, and lopinavir/ritonavir) equally across arms in Spinner et al (2020) [8]. In addition, the Spinner et al did not adjust for severity of disease.

Hospitalized patients with SpO_2 ≤94% on room air

Three RCTs comparing treatment with remdesivir (200 mg day one, 100 mg daily days 2-10) against no remdesivir treatment [5, 6, 9], and one RCT comparing five days of treatment (200 mg day one, 100 mg daily days 2-5) against 10 days (200 mg day one, 100 mg daily days 2-10) of treatment [10] served as the best available evidence among hospitalized persons with severe COVID-19 (**Table 2**, **Table 3a**, **Table 3b**). The outcomes assessed were mortality, time to

clinical improvement, need for mechanical ventilation, serious adverse events, and adverse events leading to treatment discontinuation.

All trials used different definitions of severe disease for participants. ACTT-1 participants were considered to have severe disease if they required mechanical ventilation, supplemental oxygen, if SpO_2 was 94% or lower while breathing ambient air, or if they had tachypnea (respiratory rate $\geq$24 breaths per minute) [5]. Within the SOLIDARITY trial (available only as a pre-print at this time), participants with severe disease were receiving mechanical ventilation [9]. In Wang 2020, severe participants had a SpO_2 $\leq$94% while breathing room air or a ratio of arterial oxygen partial pressure to fractional inspired O_2 of $\leq$300 mm Hg and radiologically confirmed pneumonia.

Updated analyses include the final analysis from the ACTT-1 and the interim analysis of the SOLIDARITY trial [5, 9]. SOLIDARITY reported mortality among persons remaining in hospital up to the duration of the study; however, among patients discharged before the end of the study, mortality may not have been collected completely. The study by Wang et al (2020) was stopped early due to lack of recruitment into the trial due to decreased incidence in China.

Randomization performed in Goldman 2020 failed to establish prognostic balance between baseline clinical status among the 397 patients randomized into the treatment arms, with patients in the 10-day arm more severely ill at study entry. Even with the adjusted analysis, residual confounding is possible. In addition, participants, healthcare workers, and outcome assessors were not blinded to the treatment arms.

Hospitalized patients on invasive ventilation and/or ECMO

Subgroups from SOLIDARITY and ACTT-1 reported on the outcomes of mortality, time to recovery and serious adverse events among patients on invasive ventilation or ECMO [5, 9] (**Table 3b**). The duration of ventilation at time of treatment with remdesivir was not reported in ACTT-1. This may introduce uncertainty when assessing outcomes of mortality or time to recovery.

In ACTT-1 [5], randomization was stratified by study site and disease severity at enrollment. Disease severity groups were mild to moderate COVID-19 (SpO_2 >94%) and severe COVID-19 (SpO_2 ≤94%). The severe COVID-19 stratum included patients who were hypoxemic with various degrees of severity including those requiring low flow oxygen by nasal cannula, those needing high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation and ECMO. In addition to analyses on established strata, authors performed post hoc analyses for subgroups within the strata (e.g., receiving oxygen, receiving high-flow oxygen or noninvasive mechanical ventilation, or receiving mechanical ventilation or ECMO), which may introduce concerns with risk of bias and imprecision when making inferences on efficacy of remdesivir among these subgroups including mechanically ventilated patients.

Benefits

Patients with mild-to-moderate disease who are at high risk for progression to severe COVID-19

Treatment with remdesivir for three days in ambulatory patients with mild-to-moderate COVID-19 reduced hospitalizations and COVID-19-related medically attended visits throughout day 28 (hazard ratio [HR]: 0.28; 95% confidence interval [CI]: 0.1, 0.75, low certainty of evidence [CoE]; and HR: 0.19; 95% CI: 0.07, 0.56, low CoE, respectively). No deaths were observed.

Hospitalized patients with SpO_2 ≤94% on room air

The pooled analysis failed to show a mortality benefit at 28 days (RR: 0.92; 95% CI: 0.77, 1.10; low CoE) [5, 6, 9]. Patients receiving treatment with remdesivir trend toward greater clinical improvement at 28 days than patients not receiving remdesivir (risk ratio [RR] 1.13; 95% CI: 0.91, 1.41; low CoE) [6]. In addition, based on a *post hoc* analysis of patients with severe COVID-19, receiving treatment with remdesivir had a shorter median time to recovery (median 11 vs. 18 days; rate ratio: 1.31; 95% CI: 1.12, 1.52; low CoE) and decreased need for mechanical ventilation (RR: 0.57; 95% CI: 0.42, 0.79; moderate CoE) [5].

In the study by Goldman et al that compared five and ten days of treatment, the shorter course of remdesivir showed a trend toward decreased mortality (RR: 0.75; 95% CI: 0.51, 1.12;

low CoE) and increased clinical improvement at 14 days (RR: 1.19; 95% CI: 1.01, 1.40; low CoE); however, the evidence is uncertain because the persons in the 10-day group had more severe disease at baseline and there is the possibility of residual confounding despite the adjusted analysis [10].

Hospitalized patients on invasive ventilation and/or ECMO

Treatment with remdesivir failed to show a reduction in mortality (RR: 1.23; 95% CI: 0.99, 1.53; low CoE). Similarly, remdesivir failed to show or exclude a reduction in time to recovery among patients on invasive ventilation and/or ECMO (HR: 0.98; 95% CI: 0.70, 1.36; very low CoE).

Harms

Patients with mild to moderate disease who are at high risk for progression to severe COVID-19

As with other remdesivir studies published so far, three days of remdesivir infusions did not appear to be associated with a greater risk of serious adverse events compared to no remdesivir (RR: 0.27; 95% CI: 0.1, 0.7; moderate CoE).

Hospitalized patients with SpO_2 ≤94% on room air

Patients treated with remdesivir do not appear to experience greater serious adverse events (grade 3/4) than those not receiving remdesivir (RR: 0.87; 95% CI: 0.59, 1.28; moderate CoE) [5, 6].

Patients receiving five days of remdesivir may experience fewer serious adverse events and adverse events leading to treatment discontinuation than patients receiving 10 days of remdesivir (RR: 0.61; 0.44, 0.85; low CoE and RR: 0.44; 95% CI: 0.21, 0.95; low CoE, respectively); however, this evidence is uncertain because of the increased severity of disease among patients in the 10-day arm [10].

Hospitalized patients on invasive ventilation and/or ECMO

Patients on invasive ventilation and/or ECMO treated with remdesivir do not appear to experience greater serious adverse events than those not receiving remdesivir (RR: 0.79; 95% CI: 0.54, 1.16; moderate CoE).

Other considerations

Ambulatory and hospitalized patients with mild to moderate disease who are at high risk for progression to severe COVID-19

The panel agreed that the overall certainty of evidence for the treatment of ambulatory patients was low due to concerns about imprecision, as less than half of the original projected sample size was enrolled leading to few events and fragility of the effect estimate. However, compared to prior trials, giving remdesivir early in the course of the viral infection appears to have a robust effect within the limitation of a limited sample size. The panel agreed that benefits are likely to outweigh any potential harms in patients with COVID-19 who are at high risk for severe disease. The evidence confirms that using remdesivir early in the disease process when viral loads are high confers maximum benefit. It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course.

An earlier recommendation against the initiation of remdesivir in the hospital setting for mild/moderate disease relied on post-hoc analysis of subgroup populations with variability in the timing of initiation of remdesivir relative to symptom onset, which may have contributed to the lack of a beneficial effect. Now that more direct evidence from the ambulatory population is available, the panel decided that this serves as the best available evidence to inform a recommendation for high risk hospitalized and ambulatory patients with mild-to-moderate disease within 7 days of symptom onset.

Hospitalized patients with SpO_2 ≤94% on room air

The panel agreed that the overall certainty of the evidence for treatment of persons with severe disease with remdesivir compared to no remdesivir treatment was moderate due to concerns with imprecision. Given the inconsistent definition used in the evidence to describe baseline severity, the panel recognized a knowledge gap when assessing whether greater

benefit could be attained for patients with oxygen saturation >94% and no supplemental oxygen; however, they agreed that the reported data supported the prioritization of remdesivir among persons with severe but not critical COVID-19.

The panel agreed on the overall certainty of the evidence for treatment with a five-day course compared to a 10-day course of treatment as low due to concerns with risk of bias and imprecision. The panel recognized the benefit of a shorter course of treatment, if providing similar or greater efficacy, on the availability of remdesivir. However, in a subgroup analysis of mechanically ventilated patients, the duration of treatment was 10 days in ACCT-1 trial; therefore, the panel recognized that a longer course of treatment could be desirable in this population.

Hospitalized patients on invasive ventilation and/or ECMO

The panel agreed on the overall certainty of the evidence for treatment of patients on invasive ventilation and/or ECMO with remdesivir as very low due to concerns with risk of bias and imprecision. The panel recognized that the estimates of effect for mortality and time to recovery exclude almost any benefit.

Pediatric use

The evidence for the use of remdesivir in children is limited. For ambulatory children at risk for severe disease, the RCT included 8 children aged 12 to 18 years limiting our confidence in the available direct evidence for ambulatory care.

There are no randomized controlled data assessing efficacy of remdesivir for treatment of hospitalized pediatric patients with COVID-19. A report of 77 children who received remdesivir through compassionate use early in the pandemic found good tolerability in this population with a low rate of serious adverse events [11].

An ongoing study of remdesivir in children [12] is using 5 mg/kg on day one (maximum dose 200 mg) followed by 2.5 mg/kg daily in patients over 14 days of age, gestational age more than 37 weeks, and weight greater than or equal to 2.5 kg. The U.S. Food and Drug

Administration Emergency Use Authorization applies to patients weighing over 3.5 kg and applies to the lyophilized powder formulation only.

Conclusions and research needs for this recommendation

The guideline panel suggests remdesivir for ambulatory and hospitalized patients with mild-to-moderate disease who are at high risk for severe COVID-19.

The guideline panel suggests remdesivir rather than no remdesivir for treatment of severe COVID-19 in hospitalized patients with $SpO_2 \leq 94\%$ on room air. However, the guideline panel suggests against the routine initiation of remdesivir among patients on invasive ventilation and/or ECMO. Additional clinical trials are needed to provide increased certainty about the potential for both benefit and harms of treatment with remdesivir, as well as to understand the benefit of treatment based on disease severity.

Prescribing information in the United States recommends against use of remdesivir in patients with estimated glomerular filtration rate less than 30 mL per minute. This recommendation arises from concern about accumulation of the excipient (betadex sulfobutyl ether sodium) in such patients with potential for hepatic and renal toxicity due to that substance. Additional research into safety of remdesivir in patients with reduced renal function is needed to ascertain whether this concern is substantiated.

Immunocompromised patients who are unable to control viral replication may still benefit from remdesivir despite SpO_2 that exceeds 94% on room air or a requirement for mechanical ventilation. Management of immunocompromised patients with uncontrolled viral replication is a knowledge gap and additional research into such populations is needed.

In addition, research is needed to address gaps in the evidence of effectiveness of remdesivir based on viral load.

Table 1. GRADE evidence profile, Recommendation 1

Question: Remdesivir compared to no remdesivir for ambulatory patients at high risk for progression to severe COVID-19

Last updated 12/23/2021; last reviewed 2/7/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [a]	none	0/279 (0.0%)	0/283 (0.0%)	not estimable		⨁⨁◯◯ LOW	CRITICAL
Hospitalization (all-cause) (follow-up: 28 days)												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [b]	none	5/279 (1.8%)	18/283 (6.4%)	**HR 0.28** (0.10 to 0.75)	**45 fewer per 1,000** (from 57 fewer to 16 fewer)	⨁⨁◯◯ LOW	CRITICAL
COVID-19-related medically attended visits (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [b]	none	4/246 (1.6%)	21/252 (8.3%)	**HR 0.19** (0.07 to 0.56)	**67 fewer per 1,000** (from 77 fewer to 36 fewer)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events												
1 [1]	randomized trials	not serious	not serious	not serious	serious [b]	none	5/279 (1.8%)	19/283 (6.7%)	**RR 0.27** (0.10 to 0.70)	**49 fewer per 1,000** (from 60 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio

Explanations

a. Zero events and relatively small sample size (less than half the patients of the planned sample size were enrolled).
b. Few events do not meet the optimal information size and suggest fragility in the estimate (less than half the patients of the planned sample size were enrolled).

Reference

1. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med **2021**; 386(4): 305-15.

Table 2. GRADE evidence profile, Recommendation 2

Question: Remdesivir 5 days compared to remdesivir 10 days for hospitalized patients with severe but not critical COVID-19

Last updated 9/10/2020; last reviewed 5/16/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir 5 days	remdesivir 10 days	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 [1]	randomized trials	serious [b]	not serious	not serious	serious [a]	none	16/200 (8.0%)	21/197 (10.7%)	**HR 0.75** (0.40 to 1.39)	**27 fewer per 1,000** (from 64 fewer to 42 more)	⨁⨁◯◯ LOW	CRITICAL
Clinical improvement at 14 days												
1 [1]	randomized trials	serious [b]	not serious	not serious	serious [c]	none	129/200 (64.5%)	107/197 (54.3%)	**RR 1.19** (1.01 to 1.40)	**103 more per 1,000** (from 5 more to 217 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events												
1 [1]	randomized trials	serious [b]	not serious	not serious	serious [c]	none	42/200 (21.0%)	68/197 (34.5%)	**RR 0.61** (0.44 to 0.85)	**135 fewer per 1,000** (from 193 fewer to 52 fewer)	⨁⨁◯◯ LOW	CRITICAL
Adverse events leading to treatment discontinuation												
1 [1]	randomized trials	serious [b,d]	not serious	not serious	serious [c]	none	9/200 (4.5%)	20/197 (10.2%)	**RR 0.44** (0.21 to 0.95)	**57 fewer per 1,000** (from 80 fewer to 5 fewer)	⨁⨁◯◯ LOW	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The 95% CI includes the potential for both appreciable benefit, as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
b. Goldman 2020 did not blind participants, healthcare workers or outcome assessors. After randomization, disease severity was greater in the 10-day arm; while the analysis adjusted for baseline characteristics including disease severity, there is still the potential for residual confounding.
c. The lower boundary of the 95% CI may not include a clinically meaningful effect. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
d. Goldman stratified adverse events by days 1-5, 6-10. AEs leading to treatment discontinuation during days 1-5 were 9 (4%) in the 5-day arm and 14 (7%) in the 10-day arm.

Reference

1. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med **2020;** 383: 1827-37.

Table 3a. GRADE evidence profile, Recommendation 3a

Question: Remdesivir compared to no antiviral treatment for hospitalized patients with severe COVID-19

Last reviewed and updated 5/16/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 28 days to 29 days)												
3 [1-3]	randomized trials	serious [a,b,c]	not serious	not serious	serious [d]	none	369/2726 (13.5%)	374/2593 (14.4%)	**RR 0.92** (0.77 to 1.10)	**12 fewer per 1,000** (from 33 fewer to 14 more)	⨁⨁◯◯ LOW	CRITICAL
Time to recovery (follow-up: 29 days)												
1 [2]	randomized trials	serious [c]	not serious	not serious	not serious	none	345/486 (71.0%)	306/471 (65.0%)	**Rate ratio 1.31** (1.12 to 1.52)	**97 more per 1,000** (from 41 more to 147 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical improvement (follow-up: 28 days)												
1 [1]	randomized trials	not serious [a,b]	not serious	not serious	very serious [d]	none	103/158 (65.2%)	45/78 (57.7%)	**RR 1.13** (0.91 to 1.41)	**75 more per 1,000** (from 52 fewer to 237 more)	⨁⨁◯◯ LOW	CRITICAL
Need for mechanical ventilation (follow-up: 29 days)												
1 [2]	randomized trials	not serious	not serious	not serious	serious [e]	none	52/402 (12.9%)	82/364 (22.5%)	**RR 0.57** (0.42 to 0.79)	**97 fewer per 1,000** (from 131 fewer to 47 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (grade 3/4)												
2 [1,2]	randomized trials	not serious	not serious	not serious	serious [f]	none	44/632 (7.0%)	53/545 (8.9%)	**RR 0.79** (0.54 to 1.16)	**20 fewer per 1,000** (from 45 fewer to 16 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		
Hospitalization												
1 [1]	randomized trials	not serious [a,b]	not serious	not serious	very serious [d]	none	158	78	-	MD **1 day higher** (0.12 higher to 1.88 higher)	⨁⨁◯◯ LOW	IMPORTANT
Duration of mechanical ventilation												
1 [1]	randomized trials	not serious [a,b]	not serious	not serious	serious [d]	none	158	78	-	MD **8.5 days lower** (9.14 lower to 7.86 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Co-interventions received in Wang 2020 include: interferon alpha-2b, lopinavir/ritonavir, vasopressors, antibiotics, corticosteroid therapy and were balanced between arms.
b. Wang 2020 stopped early due to lack of recruitment. Trial initiated after reduction in new patient presentation (most patients enrolled later in the disease).
c. Post hoc analysis of patients with severe disease from Pan 2020 and Beigel 2020 may introduce bias.
d. The 95% CI may not include a clinically meaningful effect.
e. Few events do not meet the optimal information size and suggest fragility in the estimate.
f. The 95% CI cannot exclude the potential for benefit or harm. Also, few events do not meet the optimal information size.

References

1. 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(10236): 1569-78.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med **2020**; 383(19): 1813-26.
3. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.

Table 3b. GRADE evidence profile, Recommendation 3b

Question: Remdesivir compared to no antiviral treatment for hospitalized patients with critical COVID-19 (IV/ECMO)

Last updated 4/5/2021; last reviewed 5/16/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 28 days to 29 days)												
2 [1,2]	randomized trials	serious [a]	not serious	not serious	serious [b,c]	none	126/385 (32.7%)	100/387 (25.8%)	**RR 1.23** (0.99 to 1.53)	**59 more per 1,000** (from 3 fewer to 137 more)	⨁⨁◯◯ LOW	CRITICAL
Time to recovery (follow-up: 29 days)												
1 [1]	randomized trials	very serious [a]	not serious	not serious	very serious [d]	none	63/131 (48.1%)	77/154 (50.0%)	**HR 0.98** (0.70 to 1.36)	**7 fewer per 1,000** (from 116 fewer to 110 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (grade 3/4)												
2 [1,3]	randomized trials	not serious	not serious	not serious [e]	serious [d]	none	44/632 (7.0%)	53/545 (9.7%)	**RR 0.79** (0.54 to 1.16)	**20 fewer per 1,000** (from 45 fewer to 16 more)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
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Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. *Post hoc* analysis of patients with severe disease from Pan 2020 and Beigel 2020 may introduce bias.
b. The 95% CI may not include a clinically meaningful effect.

c. OIS for mortality: 1682
d. The 95% CI cannot exclude the potential for benefit or harm. Also, few events do not meet the optimal information size.
e. Serious adverse events calculated from severe study groups in Beigel 2021 & Wang 2020, not invasive mechanical ventilation/ECMO subgroup.

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Supplementary Materials

Study characteristics

- **Table s1.** Remdesivir vs. no remdesivir for hospitalized patients with severe COVID-19
- **Table s2.** Remdesivir vs. no remdesivir for ambulatory patients with COVID-19

Forest plots

- **Figure s1a.** Outcome of mortality for remdesivir vs. no remdesivir for hospitalized patients with severe disease
- **Figure s1b.** Outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir for hospitalized patients with severe disease
- **Figure s1c.** Outcome of mortality for remdesivir vs. no remdesivir for hospitalized patients on invasive ventilation and/or ECMO
- **Figure s1d.** Outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir for hospitalized patients on invasive ventilation and/or ECMO

Risk of bias

- **Table s3.** Randomized controlled trials (remdesivir vs. no remdesivir)

Table s1. Should hospitalized patients with severe COVID-19 receive treatment with remdesivir vs. no remdesivir?

Study /year	Country/ Hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Beigel /2020 [1]	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore / 60 trial sites and 13 subsites	RCT	1062 (541/521)	35.6	Mean: 58.9 (15)	Met one of the following criteria suggestive of lower respiratory tract infection at the time of enrollment: radiographic infiltrates by imaging study, SpO_2 ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation	Remdesivir 200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10	(1) Placebo 200mg once day 1, 100mg once daily days 2-10	Supportive care according to the standard of care for the trial site hospital; if a hospital had a written policy or guideline for use of other treatments for COVID-19, patients could receive those treatments	Mortality at day 14 Number of recoveries Time to recovery (days) Hazard ratio of mortality Hospital discharge Adverse events	National Institute of Allergy and Infectious Diseases National Institutes of Health, Bethesda, MD Governments of Japan, Mexico, Denmark, and Singapore. Seoul National University Hospital. United Kingdom Medical Research Council

Study /year	Country/ Hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Goldman/ 2020 [2]	United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan/ 55 hospitals	RCT	397 (200/197)	N/A	N/A	Radiographic evidence of pulmonary infiltrates and either had SpO_2 of 94% or less while they were breathing ambient air or were receiving supplemental oxygen	Remdesivir (5-Day Group) 200mg once daily day 1, 100mg once daily days 2-5	(1) Remdesivir (10-Day Group): 200mg once daily day 1, 100mg once daily days 2-10	Supportive therapy received at the discretion of the investigator	Mortality at day 14 Clinical improvement (days 5, 7, 11, 14) Duration of hospitalization among patients discharge on or before day 14 Time to recovery Adverse Events	Gilead Sciences

Study /year	Country/ Hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Spinner/ 2020 [4]	United States, Europe, and Asia/ 105 hospitals	RCT	584 (193 /191 /200)	N/A	N/A	Moderate COVID-19 pneumonia (defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air)	Remdesivir (5-Day Group) 200mg once daily day 1, 100mg once daily days 2-5 via IV	(1) Remdesivir (10-Day Group): 200mg once daily day 1, 100mg once daily days 2-10 via IV (2) SoC	Steroids, HCQ, Lopinavir-ritonavir, TCZ, AZ	Day 11 clinical status on 7-point scale, No. (%) (Includes Mortality at Day 11) Clinical improvement (at Day 5, 7, 11, 14, 28) Recovery (at Day 5, 7, 11, 14, 28) Adverse Events	Gilead Sciences
Wang / 2020 [5]	China/ 10 hospitals	RCT	237 (158/78)	N/A	Median: 65 (56-71)	Hospitalized patients with pneumonia confirmed by chest imaging, SpO_2 ≤ 94% on room air, PaO_2/FIO_2 ≤ 300mmHg	Remdesivir 200mg infusion once on day 1, 100mg daily on days 2-10	(1) Placebo infusions 200mg day 1, 100mg days 2-10	Lopinavir/ritonavir, interferons, and corticosteroids	Mortality on day 28 Clinical improvement (days 7, 14, 28) Duration of invasive mechanical ventilation (days) Hospitalization days	Chinese Academy of Medical Sciences Emergency Project of COVID-19 National Key Research Development Program of China

Study /year	Country/ Hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Adverse events leading to treatment discontinuation	Beijing Science and Technology Project
WHO Solidarity Trial Consortium (Pan)/ 2021 [6]	30 countries	RCT	11266 (total) (Remdesivir 2743/2708)	38.0	N/A	Age ≥18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contraindication to any study drug	Remdesivir 200 mg once daily day 0, 100 mg once daily days 1-9	(1) SoC	Corticosteroids, convalescent plasma, anti-IL-6 drug, non-trial interferon, non-trial antiviral	Mortality at day 28 Ventilation in those not already being ventilated at the time of randomization	Participating countries covered almost all local costs and WHO covered all other study costs, receiving no extra funding

PaO_2/FIO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; **SpO_2**: oxygen saturation

Table s2. Should ambulatory patients with COVID-19 receive treatment with remdesivir vs. no remdesivir?

Study /year	Country/ Hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD)/ Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Gottlieb/ 2021 [3]	64 sites in US, Spain, Denmark, and UK	RCT	562 (279/283)	47.9	50 (15)	SARS CoV-2 PCR positive within 4 days prior to screening with at least one symptom and symptom onset for ≤7 days	Remdesivir 200 mg x 1 day, then 100 mg daily for 2 days	Placebo	None	Mortality All cause hospitalization COVID-19 related hospitalization COVID-19 related medically attended visits Change in nasopharyngeal viral load Serious adverse events	Gilead

Figure s1a. Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients with severe disease

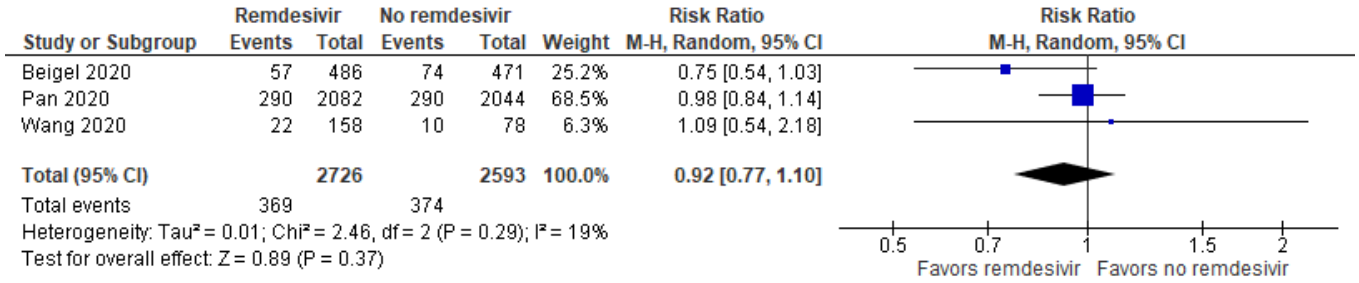

Figure s1b. Forest plot for the outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir in hospitalized patients with severe disease

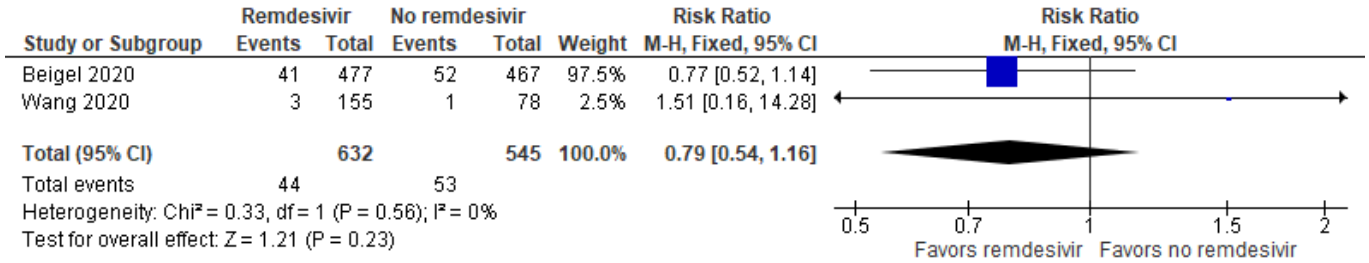

Figure s1c. Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients on invasive ventilation and/or ECMO

Figure s1d. Forest plot for the outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir in hospitalized patients on invasive ventilation and/or ECMO

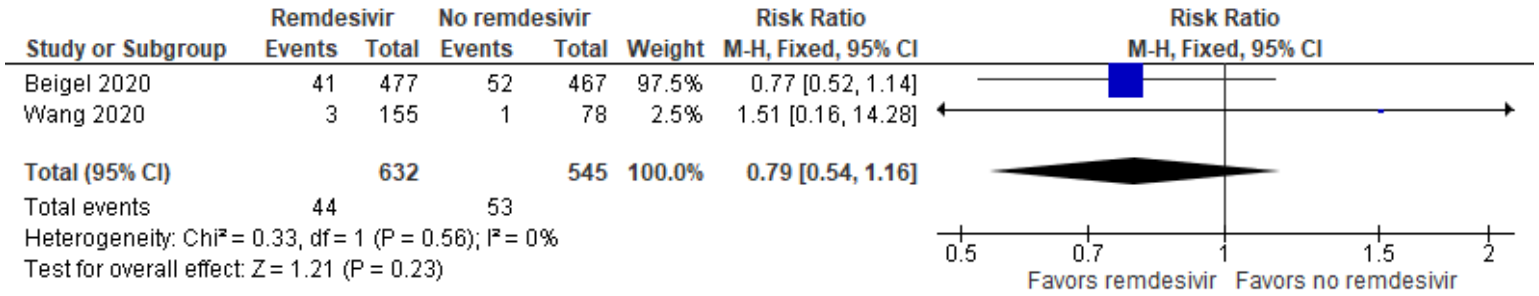

Table s3. Risk of bias for randomized controlled studies (remdesivir vs. no remdesivir)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Beigel 2020 [1]							
Goldman 2020 [2]							
Gottlieb 2021 [3]							
Spinner 2020 [4]							
Wang 2020 [5]							
WHO Solidarity Trial Consortium (Pan) 2021 [6]							

Low	High	Unclear

References for Supplementary Materials

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