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 SpO₂ ≤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

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

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 SpO₂ ≤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 $\text{SpO}_2$ 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 $\text{SpO}_2 \leq 94\%$ 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 (SpO2 >94%) and severe COVID-19 (SpO2 ≤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 SpO2 ≤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 SpO₂ ≤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 $\text{SpO}_2 \leq 94\%$ 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
Remdesivir

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 SpO₂ <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 SpO₂ 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*

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<th>Certainty</th>
<th>Importance</th>
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<td>Absolute (95% CI)</td>
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<td>Indirectness</td>
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<td>0/283 (0.0%)</td>
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<td></td>
<td>5/279 (1.8%)</td>
<td>18/283 (6.4%)</td>
<td>HR 0.28 (0.10 to 0.75)</td>
<td>45 fewer per 1,000 (from 57 fewer to 16 fewer)</td>
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<td>COVID-19-related medically attended visits (follow-up: 28 days)</td>
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<td>4/246 (1.6%)</td>
<td>21/252 (8.3%)</td>
<td>HR 0.19 (0.07 to 0.56)</td>
<td>67 fewer per 1,000 (from 77 fewer to 36 fewer)</td>
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<td>5/279 (1.8%)</td>
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<td>RR 0.27 (0.10 to 0.70)</td>
<td>49 fewer per 1,000 (from 60 fewer to 20 fewer)</td>
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**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

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*

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<th>Importance</th>
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<td><strong>Clinical improvement at 14 days</strong></td>
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<td>1 (^1) randomized trials</td>
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<td>serious (^c) none</td>
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<td><strong>Adverse events leading to treatment discontinuation</strong></td>
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<td>serious (^c) none</td>
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**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
IDSA Guideline on the Treatment and Management of COVID-19

Remdesivir

**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**

**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*

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<td>Study design</td>
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<td><strong>Time to recovery</strong> (follow-up: 29 days)</td>
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<td>a,b</td>
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<td></td>
<td></td>
<td>remdesivir</td>
<td>no remdesivir</td>
</tr>
<tr>
<td>1</td>
<td>randomized</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>trials</td>
<td>trials</td>
<td>a,b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 from the estimate of the effect.
- **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 the 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**
IDSA Guideline on the Treatment and Management of COVID-19

*Remdesivir*

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*

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Mortality (follow-up: range 28 days to 29 days)</td>
<td>2 1,2</td>
<td>randomized trials</td>
<td>serious a</td>
<td>not serious</td>
</tr>
<tr>
<td>Time to recovery (follow-up: 29 days)</td>
<td>1 1</td>
<td>randomized trials</td>
<td>very serious a</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious adverse events (grade 3/4)</td>
<td>2 1,3</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

**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; **HR:** Hazard Ratio

**Explanations**

- **Post hoc** analysis of patients with severe disease from Pan 2020 and Beigel 2020 may introduce bias.
- 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.

References


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)
IDSA Guideline on the Treatment and Management of COVID-19

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

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Country/Hospital</th>
<th>Study design</th>
<th>N subjects (intervention/comparator)</th>
<th>% female</th>
<th>Age mean (SD) / Median (IQR)</th>
<th>Severity of disease</th>
<th>Intervention (study arms)</th>
<th>Comparator</th>
<th>Co-interventions</th>
<th>Outcomes reported</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beigel /2020</td>
<td>USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore / 60 trial sites and 13 subsites</td>
<td>RCT</td>
<td>1062 (541/521)</td>
<td>35.6</td>
<td>Mean: 58.9 (15)</td>
<td>Met one of the following criteria suggestive of lower respiratory tract infection at the time of enrollment: radiographic infiltrates by imaging study, SpO2 ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation</td>
<td>Remdesivir 200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10</td>
<td>(1) Placebo 200mg once day 1, 100mg once daily days 2-10</td>
<td>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</td>
<td>Mortality at day 14, Number of recoveries, Time to recovery (days), Hazard ratio of mortality, Hospital discharge, Adverse events</td>
<td>National Institute of Allergy and Infectious Diseases, Government of Japan, Mexico, Denmark, and Singapore, Seoul National University Hospital, United Kingdom Medical Research Council</td>
</tr>
<tr>
<td>Study /year</td>
<td>Country/Hospital</td>
<td>Study design</td>
<td>N subjects (Intervention/comparator)</td>
<td>% female</td>
<td>Age mean (SD) / Median (IQR)</td>
<td>Severity of disease</td>
<td>Intervention (study arms)</td>
<td>Comparator</td>
<td>Co-interventions</td>
<td>Outcomes reported</td>
<td>Funding source</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Goldman/2020²</td>
<td>United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan/55 hospitals</td>
<td>RCT</td>
<td>397 (200/197)</td>
<td>N/A</td>
<td>N/A</td>
<td>Radiographic evidence of pulmonary infiltrates and either had SpO₂ of 94% or less while they were breathing ambient air or were receiving supplemental oxygen</td>
<td>Remdesivir (5-Day Group) 200mg once daily day 1, 100mg once daily days 2-5</td>
<td>(1) Remdesivir (10-Day Group): 200mg once daily day 1, 100mg once daily days 2-10</td>
<td>Supportive therapy received at the discretion of the investigator</td>
<td>Mortality at day 14, Clinical improvement (days 5, 7, 11, 14), Duration of hospitalization among patients discharged on or before day 14, Time to recovery, Adverse Events</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Study /year</td>
<td>Country/ Hospital</td>
<td>Study design</td>
<td>N subjects (Intervention /comparator)</td>
<td>% female</td>
<td>Age mean (SD) / Median (IQR)</td>
<td>Severity of disease</td>
<td>Intervention (study arms)</td>
<td>Comparator</td>
<td>Co-interventions</td>
<td>Outcomes reported</td>
<td>Funding source</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------</td>
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<td>--------------------------------------</td>
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<td>------------------------</td>
<td>------------</td>
<td>------------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Spinn er/ 2020</td>
<td>United States, Europe, and Asia/ 105 hospitals</td>
<td>RCT</td>
<td>584 (193 /191 /200)</td>
<td>N/A</td>
<td>N/A</td>
<td>Moderate COVID-19 pneumonia (defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation &gt;94% on room air)</td>
<td>Remdesivir (5-Day Group) 200mg once daily day 1, 100mg once daily days 2-5 via IV</td>
<td>(1) Remdesivir (10-Day Group): 200mg once daily day 1, 100mg once daily days 2-10 via IV</td>
<td>(2) SoC</td>
<td>Steroids, HCQ, Lopinavir-ritonavir, TCZ, AZ</td>
<td>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</td>
</tr>
<tr>
<td>Wang / 2020</td>
<td>China/ 10 hospitals</td>
<td>RCT</td>
<td>237 (158/78)</td>
<td>N/A</td>
<td>Median: 65 (56-71)</td>
<td>Hospitalized patients with pneumonia confirmed by chest imaging, SpO₂ ≤ 94% on room air, PaO₂/FIO₂ ≤ 300mmHg</td>
<td>Remdesivir 200mg infusion once on day 1, 100mg daily on days 2-10</td>
<td>(1) Placebo infusions 200mg day 1, 100mg days 2-10</td>
<td>Lopinavir/ritonavir, interferons, and corticosteroids</td>
<td>Mortality on day 28 Clinical improvement (days 7, 14, 28) Duration of invasive mechanical ventilation (days) Hospitalization days</td>
<td>Chinese Academy of Medical Sciences Emergency Project of COVID-19 National Key Research Development Program of China</td>
</tr>
</tbody>
</table>
### Remdesivir

<table>
<thead>
<tr>
<th>Study /year</th>
<th>Country/ Hospital</th>
<th>Study design</th>
<th>N subjects (Intervention /comparator)</th>
<th>% female</th>
<th>Age mean (SD) / Median (IQR)</th>
<th>Severity of disease</th>
<th>Intervention (study arms)</th>
<th>Comparator</th>
<th>Co-interventions</th>
<th>Outcomes reported</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Soli...</td>
<td>30 countries</td>
<td>RCT</td>
<td>11266 (total) (Remdesivir 2743/2708)</td>
<td>38.0</td>
<td>N/A</td>
<td>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</td>
<td>Remdesivir 200 mg once daily day 0, 100 mg once daily days 1-9</td>
<td>(1) SoC</td>
<td>Corticosteroids, convalescent plasma, anti-IL-6 drug, non-trial interferon, non-trial antiviral</td>
<td>Mortality at day 28 Ventilation in those not already being ventilated at the time of randomization</td>
<td>Participating countries covered almost all local costs and WHO covered all other study costs, receiving no extra funding</td>
</tr>
</tbody>
</table>

**PaO\textsubscript{2}/FIO\textsubscript{2}:** ratio of arterial oxygen partial pressure to fractional inspired oxygen; **SpO\textsubscript{2}:** oxygen saturation
### Table s2. Should ambulatory patients with COVID-19 receive treatment with remdesivir vs. no remdesivir?

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

Remdesivir

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Remdesivir Events</th>
<th>Remdesivir Total</th>
<th>No remdesivir Events</th>
<th>No remdesivir Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beigel 2020</td>
<td>57</td>
<td>456</td>
<td>74</td>
<td>471</td>
<td>25.2%</td>
<td>0.75 [0.54, 1.03]</td>
</tr>
<tr>
<td>Pan 2020</td>
<td>290</td>
<td>2082</td>
<td>280</td>
<td>2044</td>
<td>68.5%</td>
<td>0.96 [0.84, 1.14]</td>
</tr>
<tr>
<td>Wang 2020</td>
<td>22</td>
<td>158</td>
<td>10</td>
<td>76</td>
<td>3.3%</td>
<td>1.09 [0.54, 2.18]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2726</td>
<td>2593</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.92 [0.77, 1.10]</td>
</tr>
</tbody>
</table>

Total events: 398; 374
Heterogeneity: Tau² = 0.01; Chi² = 2.46, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 0.69 (P = 0.37)

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Remdesivir Events</th>
<th>Remdesivir Total</th>
<th>No remdesivir Events</th>
<th>No remdesivir Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beigel 2020</td>
<td>41</td>
<td>477</td>
<td>52</td>
<td>467</td>
<td>97.5%</td>
<td>0.77 [0.52, 1.14]</td>
</tr>
<tr>
<td>Wang 2020</td>
<td>3</td>
<td>155</td>
<td>1</td>
<td>78</td>
<td>2.5%</td>
<td>1.51 [0.16, 14.29]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>632</td>
<td>545</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.79 [0.54, 1.16]</td>
</tr>
</tbody>
</table>

Total events: 44; 53
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
**Figure s1c.** Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients on invasive ventilation and/or ECMO

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Remdesivir</th>
<th>No remdesivir</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Beigel 2020</td>
<td>23</td>
<td>131</td>
<td>29</td>
</tr>
<tr>
<td>Pan 2020</td>
<td>98</td>
<td>254</td>
<td>71</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>385</strong></td>
<td><strong>387</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events 126 100
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)

**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>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Remdesivir</th>
<th>No remdesivir</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Beigel 2020</td>
<td>41</td>
<td>477</td>
<td>52</td>
</tr>
<tr>
<td>Wang 2020</td>
<td>3</td>
<td>156</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>632</strong></td>
<td><strong>545</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events 44 53
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
### Table s3. Risk of bias for randomized controlled studies (remdesivir vs. no remdesivir)

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beigel 2020¹</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Goldman 2020²</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Gottlieb 2021³</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Spinner 2020⁴</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Wang 2020⁵</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>WHO Solidarity Trial Consortium (Pan) 2021⁶</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

- **Low**  
- **High**  
- **Unclear**
References for Supplementary Materials


