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Methods

- Approach and implications to rating the quality of evidence and strength of recommendations using GRADE methodology
**Figure 1.** Approach and implications to rating the quality of evidence and strength of recommendations using GRADE methodology *(unrestricted use of figure granted by the U.S. GRADE Network)*
Hydroxychloroquine/chloroquine & hydroxychloroquine/chloroquine + azithromycin

Evidence profiles

- Hydroxychloroquine compared to no hydroxychloroquine for hospitalized patients with COVID-19
- Hydroxychloroquine and azithromycin compared to no hydroxychloroquine/azithromycin for hospitalized patients with COVID-19
Table 1. GRADE evidence profile, Recommendation 1

**Question:** Hydroxychloroquine compared to no hydroxychloroquine for hospitalized patients with COVID-19

*Last reviewed and updated 12/23/2020*

<table>
<thead>
<tr>
<th>Mortality (RCTs) (follow up: range 22 days to 49 days)</th>
</tr>
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<tbody>
<tr>
<td><strong>№ of studies</strong></td>
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<tr>
<td>5</td>
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</table>

<table>
<thead>
<tr>
<th>Clinical status (assessed with: 7-point scale; higher signifies worsening severity)</th>
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<tr>
<td><strong>№ of studies</strong></td>
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<table>
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<tr>
<th>Progression to invasive mechanical ventilation</th>
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<th>Arrhythmias</th>
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<thead>
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<th>Adverse events, any</th>
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<td><strong>№ of studies</strong></td>
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### Certainty assessment

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<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
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<tr>
<td></td>
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<td>Hydroxy-chloroquine</td>
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<td>Relative (95% CI)</td>
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<td>Severe adverse events (assessed with: untoward medical event leading to death, a life-threatening experience, prolongation of hospitalization, or persistent or significant disability or incapacity)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>14/242 (5.8%)</td>
<td>11/237 (4.6%)</td>
<td>OR 1.26 (0.56 to 2.84)</td>
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<td></td>
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<td>QT prolongation (RCTs)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>13/89 (14.6%)</td>
<td>1/58 (1.7%)</td>
<td>RR 8.47 (1.14 to 63.03)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>QT prolongation (NRS)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46/355 (13.0%)</td>
<td>13/311 (4.2%)</td>
<td>RR 2.89 (1.62 to 5.16)</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; **OR:** Odds ratio

**Explanations**

- a. Co-interventions were provided to patients in both studies but balanced across arms.
- b. Cavalcanti 2020 excludes persons receiving supplemental oxygen at a rate of more than 4 liters per minute.
- c. The 95% CI cannot exclude the potential for no benefit or harm.
- d. Cavalcanti was an open-label trial.
e. The 95% CI includes the potential for both benefit and harm. Few events suggest the potential for fragility in the estimate.
f. Few events suggest the potential for fragility in the estimate.
g. Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
h. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
i. Did not report on blinding (including outcome adjudication committee), sequence generation or allocation concealment; Chen J 2020: all patients received nebulized alpha-interferon, 80% vs. 67.7% of subjects received Abidol in the hydroxychloroquine vs. placebo arm, respectively. Two subjects in the control arm received lopinavir/ritonavir.
j. Chen J 2020: 4 AEs include diarrhea, fatigue and transient AST elevation. Chen Z 2020: 1 rash, 1 headache. Tang 2020: 21 AEs include disease progression (1%), URI (1%), diarrhea (10%), vomiting (3%).
k. Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
l. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
m. Mahevas 2020 does not report on AEs in the comparator arm.

References
### Table 2. GRADE evidence profile, Recommendation 2

**Question:** Hydroxychloroquine and azithromycin compared to no hydroxychloroquine/azithromycin for hospitalized patients with COVID-19

*Last updated 8/20/2020; last reviewed 12/23/2020*

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>No of patients</th>
<th>Effect</th>
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<tr>
<td></td>
<td>hydroxy-</td>
<td>no hydroxy-chloroquine</td>
</tr>
<tr>
<td></td>
<td>chloroquine</td>
<td></td>
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#### Mortality (RCTs) (follow-up: range 22 days to 49 days)

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/172 (2.9%)</td>
<td>HR 0.64 (0.18 to 2.21)</td>
</tr>
<tr>
<td>6/173 (3.5%)</td>
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</tr>
</tbody>
</table>

#### Mortality (NRS)

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three non-randomized studies failed to identify an association between persons treated with HCQ + AZ and mortality: Ip reported an adjusted HR of 0.98 (95% CI: 0.75, 1.28); Magagnoli reported an adjusted HR in a subset after propensity score adjustment of 0.89 (95% CI: 0.45, 1.77); Rosenberg 2020 reported an adjusted hazard ratio (HR) of 1.35 (95% CI: 0.79, 2.40)</td>
<td></td>
</tr>
</tbody>
</table>

#### Clinical status (assessed with: 7-point scale, higher values represent worse clinical outcomes)

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>172</td>
<td>MD 0.99 higher (0.57 higher to 1.73 higher)</td>
</tr>
<tr>
<td>173</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Virologic failure (follow-up: range 5 days to 6 days; assessed with: PCR test)

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>29/71 (40.8%)</td>
<td>RR 8.50 (1.16 to 62.31)</td>
</tr>
<tr>
<td>12/12 (100.0%)</td>
<td>129 more per 1,000 (from 3 more to 1,000 more)</td>
</tr>
</tbody>
</table>

#### QT prolongation (RCTs)

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/116 (14.7%)</td>
<td>RR 8.50 (1.16 to 62.31)</td>
</tr>
<tr>
<td>1/58 (1.7%)</td>
<td>129 more per 1,000 (from 3 more to 1,000 more)</td>
</tr>
</tbody>
</table>
### Certainty assessment

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Vehydroxy-chloroquine</th>
<th>no hydroxy-chloroquine</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
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<tr>
<td>QT prolongation (NRS)</td>
<td>2</td>
<td>observational studies</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>10/95 (10.5%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>🌟🌟🌟🌟</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1</td>
<td>randomized trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>5/239 (2.1%)</td>
<td>0/50 (0.0%)</td>
<td>RR 2.34 (0.13 to 41.61)</td>
<td>0 fewer per 1,000 (from 0 fewer to 0 fewer)</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.
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### 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. Co-interventions were provided to patients but balanced across arms. Cavalcanti 2020 was open label; however, likely did not influence the outcome of mortality.
- b. Cavalcanti 2020 excludes persons receiving supplemental oxygen at a rate of more than 4 liters per minute.
- c. A very small number of events. Optimal information size not met.
- d. The 95% CI includes the potential for both benefit and harm.
- e. Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
- f. Cavalcanti was an open-label trial.
- g. Optimal information size not met.
- h. No contemporaneous control groups; no adjustment for baseline severity, resulting in high risk for residual confounding
- i. Two case series from France showed divergent results
- j. Surrogate marker for mortality or resolution of COVID-19.
- k. Gautret reported 21/61 patients as positive at day 6 (estimate from supplied graph); Molina reported 8/10 patients positive at day 5 or 6. Pooled rates of virologic failure using fixed effects inverse variance method resulted in a 43% failure rate (95% CI, 32% to 54%)
Gautret reported on a historical viral clearance rate in symptomatic patients from a separate hospital. Criteria for selection of patients remains unclear, as presumably a sizable number of untreated patients could have been available with data on viral clearance.

Indirect measure of arrhythmia-specific mortality.

Azithromycin and hydroxychloroquine can independently cause QT prolongation. Used together there can be an additive effect. Caution should be exercised with other agents known to prolong the QT interval.

Molina 2020: 1/11 leading to treatment discontinuation; Chorin 2020: 9/84 with significant QTc prolongation of more than 500 ms.

Azithromycin and hydroxychloroquine can independently cause QT prolongation. Used together there can be an additive effect. Caution should be exercised with other agents known to prolong the QT interval.

Molina 2020: 1/11 leading to treatment discontinuation; Chorin 2020: 9/84 with significant QTc prolongation of more than 500 ms.

Cavalcanti 2020 serious adverse events included pulmonary embolism, QTc prolongation, myocardial infarction, abdominal-wall hemorrhage.

References
Hydroxychloroquine as post-exposure prophylaxis

Evidence profiles

- Hydroxychloroquine compared to no hydroxychloroquine for post-exposure prophylaxis of COVID-19
Table 3. GRADE evidence profile, Recommendation 3

**Question:** Hydroxychloroquine compared to no hydroxychloroquine for post-exposure prophylaxis of COVID-19

*New evidence profile developed 9/23/2021*

<table>
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<tr>
<th>Certainty assessment</th>
<th>Nr of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
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<tr>
<td>Nr of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>3 1 2 3 randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
</tr>
<tr>
<td>3 1 2 3 randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious b</td>
</tr>
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<td>3 1 2 3 randomized trials</td>
<td>not serious</td>
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<td>not serious</td>
<td>very serious b</td>
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<td>3 1 2 3 randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious b</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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**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. Boulware included both laboratory-confirmed COVID-19 as well as probable COVID-19; 11/49 patients receiving HCQ were laboratory confirmed and 9/58 receiving placebo were laboratory confirmed.
b. The 95% CI includes both the potential of benefit and the risk of harm.

References
Lopinavir/ritonavir

Evidence profiles

- Prophylactic lopinavir/ritonavir compared to no prophylactic lopinavir/ritonavir for persons exposed to COVID-19
- Lopinavir/ritonavir compared to no lopinavir/ritonavir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease
- Lopinavir/ritonavir compared to no lopinavir/ritonavir for hospitalized patients with severe COVID-19
### Table 4. GRADE evidence profile, Recommendation 4

**Question:** Prophylactic lopinavir/ritonavir compared to no prophylactic lopinavir/ritonavir for persons exposed to COVID-19

*New evidence profile developed 2/16/2022*

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<th>Certainty</th>
<th>Importance</th>
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</thead>
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<td>Nr of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Incocnsistency</td>
</tr>
<tr>
<td>Symptomatic SARS-COV-2 infection (COVID-19) regardless of baseline PCR/serology (follow-up: 21 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Symptomatic SARS-COV-2 infection (COVID-19), negative PCR and serology at baseline (follow-up: 21 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Adverse events (follow-up: 29 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>serious c</td>
<td>not serious</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
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</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
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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 has not been peer reviewed or published.

**CI:** Confidence interval; **HR:** Hazard ratio; **PCR:** Polymerase chain reaction; **RR:** Risk ratio

**Explanations**
- a. Few events, unable to exclude benefits as well as harms
- b. This pre-specified primary endpoint adjusted analysis is a mixed model analysis adjusted for baseline imbalance
- c. Participants not blinded to lopinavir/ritonavir
- d. Two serious adverse events occurred and both judged by the author as unrelated to lopinavir/ritonavir

**Reference**
Table 5. GRADE evidence profile, Recommendation 5

**Question:** Lopinavir/ritonavir compared to no lopinavir/ritonavir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

*New evidence profile developed 2/16/2022*

<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>
</tbody>
</table>

### Mortality (follow-up: 90 days)

**1** randomized trials

<table>
<thead>
<tr>
<th></th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>lopinavir/ritonavir</th>
<th>no lopinavir/ritonavir</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>not serious</td>
<td>not serious</td>
<td>very serious a</td>
<td>none</td>
<td>2/244 (0.8%)</td>
<td>1/227 (0.4%)</td>
<td>RR 1.86 (0.17 to 20.40)</td>
<td>4 more per 1,000 (from 4 fewer to 85 more)</td>
<td>✭✭✭</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

### COVID-19-related hospitalizations (follow-up: 90 days)

**1** randomized trials

<table>
<thead>
<tr>
<th></th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>lopinavir/ritonavir</th>
<th>no lopinavir/ritonavir</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>not serious</td>
<td>not serious</td>
<td>serious a</td>
<td>none</td>
<td>14/244 (5.7%)</td>
<td>11/227 (4.8%)</td>
<td>HR 1.16 (0.53 to 2.56)</td>
<td>8 more per 1,000 (from 22 fewer to 71 more)</td>
<td>✭✭✭✭</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

### Serious adverse events (follow-up: 90 days)

**1** randomized trials

<table>
<thead>
<tr>
<th></th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>lopinavir/ritonavir</th>
<th>no lopinavir/ritonavir</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>not serious</td>
<td>not serious</td>
<td>serious a</td>
<td>none</td>
<td>20/232 (8.6%)</td>
<td>12/220 (5.5%)</td>
<td>RR 1.58 (0.79 to 3.16)</td>
<td>32 more per 1,000 (from 11 fewer to 118 more)</td>
<td>✭✭✭✭</td>
<td>CRITICAL</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 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 has not been peer reviewed or published.

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

**Explanations**
- a. Sparse data, few events, unable to excluded harms as well as benefits

**References**

Table 6. GRADE evidence profile, Recommendation 6

**Question:** Lopinavir/ritonavir compared to no lopinavir/ritonavir for hospitalized patients with severe COVID-19

*Last reviewed and updated 11/22/2020*

<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></td>
<td></td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
</tbody>
</table>

**Mortality (follow up: 28 days)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>lopinavir/ritonavir</th>
<th>placebo</th>
<th>RR 1.00</th>
<th>0 fewer per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 1,2,3</td>
<td>randomized trials</td>
<td>not serious a</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>538/3111 (17.3%) c</td>
<td>938/4896 (19.2%)</td>
<td>RR 1.00 (0.89 to 1.13)</td>
<td>0 fewer per 1,000 (from 21 fewer to 25 more)</td>
</tr>
</tbody>
</table>

**Invasive mechanical ventilation (follow up: 28 days)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>lopinavir/ritonavir</th>
<th>placebo</th>
<th>RR 1.12</th>
<th>11 more per 1,000 (from 6 fewer to 30 more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 1,3</td>
<td>randomized trials</td>
<td>serious a,d</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>166/1655 (10.0%)</td>
<td>297/3380 (8.8%)</td>
<td>RR 1.12 (0.93 to 1.34)</td>
<td>11 more per 1,000 (from 6 fewer to 30 more)</td>
</tr>
</tbody>
</table>

**Adverse events leading to treatment discontinuation**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>lopinavir/ritonavir</th>
<th>placebo</th>
<th>RR 0.78</th>
<th>154 fewer per 1,000 (from 21 fewer to 266 fewer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1</td>
<td>randomized trials</td>
<td>serious a</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious e</td>
<td>none</td>
<td>54/99 (54.5%)</td>
<td>70/100 (70.0%)</td>
<td>RR 0.78 (0.62 to 0.97)</td>
<td>154 fewer per 1,000 (from 21 fewer to 266 fewer)</td>
</tr>
</tbody>
</table>

**Failure of clinical improvement at 14 days (follow up: 14 days)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>lopinavir/ritonavir</th>
<th>placebo</th>
<th>RR 0.78</th>
<th>154 fewer per 1,000 (from 21 fewer to 266 fewer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1</td>
<td>randomized trials</td>
<td>serious a</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious f</td>
<td>none</td>
<td>54/99 (54.5%)</td>
<td>70/100 (70.0%)</td>
<td>RR 0.78 (0.62 to 0.97)</td>
<td>154 fewer per 1,000 (from 21 fewer to 266 fewer)</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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- **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.
IDSA Guideline on the Treatment and Management of COVID-19
Tables and Figures

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Study limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inconsistency</td>
<td>Unexplained heterogeneity across study findings</td>
</tr>
<tr>
<td>Indirectness</td>
<td>Applicability or generalizability to the research question</td>
</tr>
<tr>
<td>Imprecision</td>
<td>The confidence in the estimate of an effect to support a particular decision</td>
</tr>
<tr>
<td>Publication bias</td>
<td>Selective publication of studies</td>
</tr>
</tbody>
</table>

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. Unblinded studies which can affect outcomes that require judgment, such as how investigators judge clinical improvement or decide to stop the treatment in patients with side effects.
b. 95% CI may not include a meaningful difference.
c. Modified intention to treat data from Cao 2020 used for this outcome; some deaths were excluded when drug was not given.
d. One patient randomized to the lopinavir-ritonavir arm in Cao 2020 was mechanically ventilated at baseline.
e. Small number of events making estimates highly uncertain
f. The upper boundary of the 95% confidence interval crosses the threshold of meaningful improvement as the worst case estimate is a 3% RRR.

References
Glucocorticoids

Evidence profiles

- Glucocorticoids compared to no glucocorticoids for critically ill patients with COVID-19
- Glucocorticoids compared to no glucocorticoids for hospitalized patients with severe but not critical COVID-19
- Glucocorticoids compared to no glucocorticoids for hospitalized patients with COVID-19 not receiving supplemental oxygen
### Table 7. GRADE evidence profile, Recommendation 7

**Question:** Glucocorticoids compared to no glucocorticoids for critically ill patients with COVID-19

**Last reviewed and updated 9/25/2020**

<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><strong>Mortality (follow up: 28 days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 1 randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>280/749 (37.4%)</td>
<td>OR 0.66 (0.54 to 0.82)</td>
</tr>
<tr>
<td>Hospital discharge (follow up: 28 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 2 randomized trials</td>
<td>not serious a</td>
<td>not serious</td>
<td>1360/2104 (64.6%)</td>
<td>RR 1.11 (1.04 to 1.19)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 1 randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>6 trials reported 64 events among 354 patients randomized to corticosteroids and 80 events among 342 patients randomized to standard care (Stern 2020).</td>
<td>⨁⨁⨁ MODERATE CRITICAL</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
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**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; **OR:** Odds ratio; **RR:** Risk ratio

**Explanations**

- a. Analysis adjusted for baseline age.
- b. Indirectness due to different health care system (allocation of intensive care resources in an unblinded study). Indirectness to other corticosteroids.
- c. The 95% CI includes the potential for both harm as well as benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

**References**

**Table 8. GRADE evidence profile, Recommendation 8**

**Question:** Glucocorticoids compared to no glucocorticoids for hospitalized patients with severe but not critical COVID-19

*Last reviewed and updated 9/25/2020*

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Mortality (follow up: 28 days)</td>
<td>1 randomized trials</td>
<td>not serious a</td>
<td>not serious</td>
<td>serious b</td>
</tr>
<tr>
<td>Hospital discharge (follow up: 28 days)</td>
<td>1 randomized trials</td>
<td>not serious a</td>
<td>not serious</td>
<td>serious b</td>
</tr>
</tbody>
</table>

**Adverse events**

Patients receiving a short course of steroids may experience hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of infection (Salton 2020; Henzen 2000; Siemieniuk 2015).

**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. Analysis adjusted for baseline age.
- b. Indirectness due to different health care system (allocation of intensive care resources in an unblinded study). Indirectness to other corticosteroids.

**Reference**

Table 9. GRADE evidence profile, Recommendation 9

**Question:** Glucocorticoids compared to no glucocorticoids for hospitalized patients with COVID-19 not receiving supplemental oxygen

*Last reviewed and updated 9/25/2020*

### Certainty assessment

| & # of studies & Study design & Risk of bias & Inconsistency & Indirectness & Imprecision & Other considerations | & Nº of patients & & Relative (95% CI) & Absolute (95% CI) & & Certainty & Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mortality (follow up: 28 days) | 1 & randomized trials & serious | not serious | not serious | serious | none | 85/501 (17.0%) & 137/1034 (13.2%) | RR 1.22 (0.93 to 1.61) | 29 more per 1,000 (from 9 fewer to 81 more) | ⬤ ⬤ ⬤ ⬤ LOW | CRITICAL |
| Hospital discharge (follow up: 28 days) | 1 & randomized trials & serious | not serious | not serious | serious | none | 366/501 (73.1%) & 791/1034 (76.5%) | RR 0.99 (0.87 to 1.12) | 8 fewer per 1,000 (from 99 fewer to 92 more) | ⬤ ⬤ ⬤ ⬤ LOW | IMPORTANT |

### Adverse events

Patients receiving a short course of steroids may experience: hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of infection (Salton 2020; Henzen 2000; Siemieniuk 2015).

### 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. Risk of bias due to post hoc subgroup effect among persons not receiving supplemental oxygen.
- b. The 95% CI includes the potential for appreciable harm and cannot exclude the potential for benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
- c. The 95% CI cannot exclude the potential for either appreciable harm or benefit.

### Reference

Inhaled corticosteroids

Evidence profiles

- Inhaled corticosteroids compared to no inhaled corticosteroids for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease
### Table 10. GRADE evidence profile compared to no inhaled corticosteroids for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

**Question:** Inhaled corticosteroids compared to no inhaled corticosteroids for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

Last reviewed and updated 10/10/2022

<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><strong>Mortality</strong> (follow-up: range 14 days to 30 days)</td>
<td>7</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Hospitalizations</strong> (follow-up: range 14 days to 30 days)</td>
<td>6</td>
<td>randomized trials</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong> (follow-up: range 14 days to 30 days)</td>
<td>5</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 has not been peer reviewed or published.

**CI:** confidence interval; **RR:** risk ratio

**Explanations**

- a. Agusti 2022, Duvignaud 2022, Ramakrishnan 2021, Yu 2021 were open-label trials, which may introduce bias into outcomes subjectively measured, such as COVID-19-related hospitalizations and SAEs.
- b. 8/35 patients in Song 2021 received HCQ in addition to ciclesonide. All patients in Song 2021 had mild-to-moderate COVID-19 and were hospitalized.
- c. Sparse data, few events, unable to excluded harms as well as benefits
d. In Yu 2021 the following patients were admitted to hospital without need for supplemental oxygen: budesonide 17/787 (2%) placebo 21/799 (3%).

References
Interleukin-6 inhibitors

Evidence profiles

- Tocilizumab compared to no tocilizumab for hospitalized patients with COVID-19
- Sarilumab compared to no sarilumab for hospitalized patients with COVID-19
Table 11. GRADE evidence profile, Recommendation 11

**Question:** Tocilizumab compared to no tocilizumab for hospitalized patients with COVID-19

*Last updated 2/17/2021; last reviewed 9/14/2021*

<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 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effect</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong> (follow-up: range 28 days to 30 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 ¹ ³ ⁸ randomized trials</td>
<td>not serious a</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
</tr>
<tr>
<td><strong>Clinical deterioration</strong> (follow-up: range 14 days to 30 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 ¹ ³ ⁸ randomized trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious d</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 ¹ ³ ⁸ randomized trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>serious f</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

**Explanations**

- a. Although some studies did not blind participants or investigators, this is unlikely to affect the mortality outcome.
- b. 95% CI includes benefits as well as harms.
- c. Some studies lacked blinding and due to the mechanism of tocilizumab (reduction in inflammatory marker), unblinding likely occurred in the blinded studies.
d. Definition of clinical deterioration varied, with all studies including need for ventilation and death, but other studies included need for ICU admission (2 studies) or PaO₂/FiO₂ ratio of less than 150 mmHg (1 study).

e. The 95% CI includes both potential for harm as well as benefit; Few events reported do not meet the optimal information size and suggest fragility in the estimate.

References

Table 12. GRADE evidence profile, Recommendation 12

**Question:** Sarilumab compared to no sarilumab for hospitalized patients with COVID-19

**New evidence profile developed 9/14/2021**

<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 (assessed with: indirect estimate from network meta-analysis)</td>
<td>18 1,2</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Clinical deterioration (follow-up: 21 days; assessed with: progression to intubation, ECMO, or death)</td>
<td>2 2,3</td>
<td>randomized trials</td>
<td>serious c</td>
<td>not serious d</td>
</tr>
<tr>
<td>Serious adverse events (follow-up: 21 days)</td>
<td>4 2,4</td>
<td>randomized trials</td>
<td>serious c</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; **OR:** Odds ratio; **RR:** Risk ratio

**Explanations**

- a. 18 trials included in the network.
- b. The direct network estimate crosses the line of no effect; however, the indirect estimate in the network demonstrates a trend toward mortality reduction when sarilumab + corticosteroids rather than corticosteroids alone is given. Few events reported in the direct network estimate suggesting fragility.
- c. Lack of blinding of study personnel, participants, and outcome assessors.
d. Substantial heterogeneity present (I²=57%); however, likely contributes to the wide CI and accounted for within imprecision.

e. Definition of clinical deterioration varied, with all studies including need for ventilation; however, one study included ECMO and death and the other study included use of high-flow cannula.

f. 95% CI cannot exclude the possibility of harm. Few events suggest fragility of the estimate.

g. Analysis includes participants free of invasive mechanical ventilation at baseline for Gordon and patients free of high-flow cannula at baseline.

h. 95% CI cannot exclude the possibility of harms.

References


Convalescent plasma

Evidence profiles

- Convalescent plasma compared to no convalescent plasma for hospitalized patients with COVID-19
- Convalescent plasma compared to no convalescent plasma for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease
Table 13. GRADE evidence profile, Recommendation 13

**Question:** Convalescent plasma compared to no convalescent plasma for hospitalized patients with COVID-19

**Last reviewed and updated 11/4/2021**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Nr of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Mortality (RCTs) (follow-up: range 15 days to 60 days)</td>
<td>18</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>4</td>
<td>randomized trials</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious adverse events (transfusion-associated circulatory overload, transfusion-related acute lung injury, severe allergic transfusion reaction) (follow-up: 4 hours)</td>
<td>1</td>
<td>observational studies</td>
<td>extremely serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious adverse events (mortality, cardiac, thrombotic, sustained hypotensive events requiring intervention) (follow-up: 7 days)</td>
<td>1</td>
<td>observational studies</td>
<td>extremely serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Any adverse events (RCTs)</td>
<td>11</td>
<td>randomized trials</td>
<td>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 the effect |

**Risk of bias:** Study limitations

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

**References**


**Explanations**

a. Li 2020 time between symptom onset and randomization was over 14 days for >90% (median 30 days), no adjustment for co-interventions, allocation concealment methods not reported and participants and healthcare professionals not blinded.

b. Many trials had concerns due to open-label trial, allocation concealment not reported, and no adjustments for co-interventions. Differences between study protocol and published report (e.g., inclusion criteria, outcomes, intervention groups) noted for Pouladzadeh 2021.

c. The 95% CI includes the potential for appreciable benefit; however, cannot exclude the potential for no effect.

d. Concerns include open-label trial design and assessment of outcome.

e. The 95% CI may not include a clinically meaningful reduction in need for mechanical ventilation.

f. No comparative effects available. Some subjectivity in classification of outcomes as transfusion related.

g. Lack standard definition for adverse events. Studies report on mild to severe events.

h. The 95% CI includes the potential for both increased harms, as well as no increased harms.

**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; **OR:** Odds ratio; **SAEs:** Serious adverse events


### Table 14. GRADE evidence profile, Recommendation 14

**Question:** Convalescent plasma compared to no convalescent plasma for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

*Last reviewed and updated 1/21/2022*

<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 patients</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>convalescent plasma</td>
<td>no convalescent plasma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**All-cause mortality (follow-up: range 15 days to 28 days)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>cert</th>
<th>imp</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious</td>
<td>none</td>
<td>□□□□□</td>
<td>□□□□□</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

|          |          | RR 0.53 | (0.14 to 1.98) | 4 fewer per 1,000 (from 7 fewer to 7 more) | |
|          |          | (95% CI) | | |

**COVID-19 related hospitalizations, ED/urgent care visits, or death (follow-up: 15 days)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>cert</th>
<th>imp</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>□□□□□</td>
<td>□□□□□</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

|          |          | RR 0.79 | (0.62 to 1.00) | 29 fewer per 1,000 (from 53 fewer to 0 fewer) | |
|          |          | (95% CI) | | |

**Hospitalizations (all-cause) (follow-up: range 15 days to 28 days)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
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<th>imp</th>
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<tbody>
<tr>
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<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>□□□□□</td>
<td>□□□□□</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

|          |          | RR 0.74 | (0.56 to 0.98) | 29 fewer per 1,000 (from 50 fewer to 2 fewer) | |
|          |          | (95% CI) | | |

**Progression to severe respiratory disease (follow-up: 15 days; assessed with: defined as a respiratory rate of ≥30 breaths per minute, SaO₂ < 93% on room air, or both)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>cert</th>
<th>imp</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>□□□□□</td>
<td>□□□□□</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

|          |          | RR 0.52 | (0.29 to 0.94) | 150 fewer per 1,000 (from 222 fewer to 19 fewer) | |
|          |          | (95% CI) | | |

**Serious adverse events: serious transfusion reactions (requiring treatment or admission) (follow-up: 15 days)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>cert</th>
<th>imp</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious</td>
<td>none</td>
<td>□□□□□</td>
<td>□□□□□</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

|          |          | RR 5.95 | (0.72 to 49.29) | 6 more per 1,000 (from 1 more to 11 more) | |
|          |          | (95% CI) | | |

**Any adverse events (follow-up: 15 days)**

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>cert</th>
<th>imp</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>□□□□□</td>
<td>□□□□□</td>
<td>IMPORTANT</td>
</tr>
</tbody>
</table>

|          |          | RR 0.86 | (0.70 to 1.05) | 24 fewer per 1,000 (from 52 fewer to 9 more) | |
|          |          | (95% CI) | | |
IDSA Guideline on the Treatment and Management of COVID-19

Tables and Figures

<table>
<thead>
<tr>
<th>GRADE Working Group grades of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High certainty:</strong> We are very confident that the true effect lies close to that of the estimate of the effect</td>
</tr>
<tr>
<td><strong>Moderate certainty:</strong> 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</td>
</tr>
<tr>
<td><strong>Low certainty:</strong> Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect</td>
</tr>
<tr>
<td><strong>Very low certainty:</strong> We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Risk of bias: Study limitations</th>
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<tbody>
<tr>
<td><strong>Inconsistency:</strong> Unexplained heterogeneity across study findings</td>
</tr>
<tr>
<td><strong>Indirectness:</strong> Applicability or generalizability to the research question</td>
</tr>
<tr>
<td><strong>Imprecision:</strong> The confidence in the estimate of an effect to support a particular decision</td>
</tr>
<tr>
<td><strong>Publication bias:</strong> Selective publication of studies</td>
</tr>
</tbody>
</table>

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

**CI:** Confidence interval; **ED:** Emergency department; **RR:** Risk ratio; **SaO$_2$:** Saturated oxygen

**Explanations**

- a. Deaths beyond 15 days and up to 30 days: an additional 5 deaths occurred in the plasma group and 1 death in placebo (normal saline) group.
- b. Only one event.
- c. 95% CI includes benefits as well as harms; OIS not met.
- d. Few events reported. 95% CI may not include clinically meaningful benefit.
- e. Trial was terminated early due to futility.
- f. Oxygenation and respiration rates are surrogate measures of need for ventilation, morbidity and death.
- g. Few events reported do not meet the optimal information size and suggest fragility of the estimate.
- h. Using 0.5 event continuity correction.
- i. Zero events in the control group. Absolute risk difference not informed by relative risk

**References**

Remdesivir

Evidence profiles

- Remdesivir compared to no remdesivir for ambulatory patients at high risk for severe COVID-19
- Remdesivir 5 days compared to remdesivir 10 days for hospitalized patients with severe but not critical COVID-19
- Remdesivir compared to no antiviral treatment for hospitalized patients with severe COVID-19
- Remdesivir compared to no antiviral treatment for hospitalized patients with critical COVID-19 (IV/ECMO)
Table 15. GRADE evidence profile, Recommendation 15

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

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

<table>
<thead>
<tr>
<th>Mortality (follow-up: 28 days)</th>
<th>Certainty assessment</th>
<th>No. of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td>No. of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td></td>
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<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospitalization (all-cause) (follow-up: 28 days)</th>
<th>Certainty assessment</th>
<th>No. of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COVID-19-related medically attended visits (follow-up: 28 days)</th>
<th>Certainty assessment</th>
<th>No. of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious adverse events</th>
<th>Certainty assessment</th>
<th>No. of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</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; **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 16. GRADE evidence profile, Recommendation 16

**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*

<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>Remdesivir 5 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remdesivir 10 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mortality**

<table>
<thead>
<tr>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>16/200 (8.0%)</td>
<td>HR 0.75 (0.40 to 1.39)</td>
<td>LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>21/197 (10.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical improvement at 14 days**

<table>
<thead>
<tr>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>129/200 (64.5%)</td>
<td>RR 1.19 (1.01 to 1.40)</td>
<td>LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>107/197 (54.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Serious adverse events**

<table>
<thead>
<tr>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>42/200 (21.0%)</td>
<td>RR 0.61 (0.44 to 0.85)</td>
<td>LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>68/197 (34.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adverse events leading to treatment discontinuation**

<table>
<thead>
<tr>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/200 (4.5%)</td>
<td>RR 0.44 (0.21 to 0.95)</td>
<td>LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>20/197 (10.2%)</td>
<td></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.

**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
### Table 17a. GRADE evidence profile, Recommendation 17a

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

*Last reviewed and updated 5/16/2021*

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
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<tr>
<td></td>
<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td><strong>Mortality (follow-up: range 28 days to 29 days)</strong></td>
<td>3 ¹-³</td>
<td>randomized trials</td>
<td>serious ᵃ ᵇ ᶜ</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Time to recovery (follow-up: 29 days)</strong></td>
<td>¹ ²</td>
<td>randomized trials</td>
<td>serious ᶜ</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Clinical improvement (follow-up: 28 days)</strong></td>
<td>¹ ¹</td>
<td>randomized trials</td>
<td>not serious ᵃ ᵇ</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Need for mechanical ventilation (follow-up: 29 days)</strong></td>
<td>¹ ²</td>
<td>randomized trials</td>
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<td>not serious</td>
</tr>
<tr>
<td><strong>Serious adverse events (grade 3/4)</strong></td>
<td>² ¹ ²</td>
<td>randomized trials</td>
<td>not serious ᵃ ᵇ</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td>¹ ¹</td>
<td>randomized trials</td>
<td>not serious ᵃ ᵇ</td>
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### Tables and Figures

#### Certainty assessment

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<th>Nr of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>remdesivir</th>
<th>no remdesivir</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>158</td>
<td>78</td>
<td>MD 8.5 days lower</td>
<td>(9.14 lower to 7.86 lower)</td>
<td>○○○○ MODERATE</td>
<td>IMPORTANT</td>
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</tr>
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</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 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**

### Table 17b. GRADE evidence profile, Recommendation 17b

**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

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<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nr of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (^1) 2 (^2)</td>
<td>randomized trials</td>
<td>serious (^a)</td>
<td>not serious</td>
<td>not serious</td>
<td>serious (^b,c)</td>
<td>none</td>
<td>remdesivir</td>
<td>126/385 (32.7%)</td>
<td>no remdesivir</td>
<td>Relative (95% CI)</td>
</tr>
<tr>
<td>Mortality (follow-up: range 28 days to 29 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (^1)</td>
<td>randomized trials</td>
<td>very serious (^a)</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious (^d)</td>
<td>none</td>
<td>remdesivir</td>
<td>63/131 (48.1%)</td>
<td>no remdesivir</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Time to recovery (follow-up: 29 days)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (^1) 3 (^3)</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious (^e)</td>
<td>serious (^d)</td>
<td>none</td>
<td>remdesivir</td>
<td>44/632 (7.0%)</td>
<td>no remdesivir</td>
<td>Relative (95% CI)</td>
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<td>Serious adverse events (grade 3/4)</td>
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</table>

**GRADE Working Group grades of evidence**

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**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**

- 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 2020 & Wang 2020, not invasive mechanical ventilation/ECMO subgroup.

References

Famotidine

Evidence profiles

- Famotidine compared to no famotidine for ambulatory patients with mild-to-moderate COVID-19
Table 18. GRADE evidence profile, Recommendation 18

**Question:** Famotidine compared to no famotidine for ambulatory patients with mild-to-moderate COVID-19

**New evidence profile developed 5/17/2022**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Nr of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
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<td>Nr of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
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<td>Symptom resolution (follow-up: 28 days) a</td>
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<tr>
<td>Adverse events d</td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
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</table>

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**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. Time to symptom resolution was the primary end point. However, the authors reported a faster (earlier) rate of symptom resolution with famotidine. No deaths were encountered.
- b. Sparse data, few events and small sample size
- c. Only p-value reported; number of events estimated from survival curve graph.
- d. No serious adverse events were encountered. Transaminase elevation in 1 patient in both arms; nausea / vomiting in 1 patient with famotidine; thrombocytopenia and hives in 1 patient each in the placebo group.

**Reference**

### Table 19. GRADE evidence profile, Recommendation 19

**Question:** Famotidine compared to no famotidine for hospitalized patients with severe COVID-19

*Last reviewed and updated 5/17/2022*

<table>
<thead>
<tr>
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<th>Certainty</th>
<th>Importance</th>
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<td>Absolute (95% CI)</td>
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<td>not serious</td>
<td>serious&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><strong>Mechanical ventilation</strong></td>
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<td></td>
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<td>1&lt;sup&gt;st&lt;/sup&gt; randomized trials</td>
<td>serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious</td>
<td>not serious</td>
<td>serious&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>not serious</td>
<td>not serious</td>
<td>serious&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Time to symptom-free</strong></td>
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<td>serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious</td>
<td>not serious</td>
<td>serious&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><strong>Length of hospital stay</strong></td>
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<td>not serious</td>
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<td>Indirectness</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; **MD:** Mean difference; **RR:** Risk ratio

**Explanations**

a. Unclear allocation concealment in an unblinded study

b. Sparse data, small number of events or patients

**Reference**

Janus kinase inhibitors

Evidence profiles

- Baricitinib compared to no baricitinib for hospitalized patients receiving standard of care for severe COVID-19
- Baricitinib compared to no baricitinib for critically ill (OS-7) patients with COVID-19 pneumonia requiring invasive mechanical ventilation
- Baricitinib with remdesivir compared to remdesivir for hospitalized patients with COVID-19
- Tofacitinib compared to no tofacitinib for hospitalized patients with COVID-19
Table 20. GRADE evidence profile, Recommendation 20

**Question:** Baricitinib compared to no baricitinib for hospitalized patients receiving standard of care for severe COVID-19

*Last reviewed and updated 4/29/2022*

<table>
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<tr>
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<th>Certainty</th>
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<td>Nº 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 60 days)</td>
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<td>randomized trials</td>
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<td>not serious</td>
</tr>
<tr>
<td>Mechanical ventilation (follow-up: 28 days)</td>
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<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
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<td>13</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious adverse events (follow-up: 28 days)</td>
<td>13</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; HR: Hazard Ratio; OR: Odds ratio; RR: Risk ratio

Explanations
a. 95% CI cannot exclude no benefit.
b. Multiple imputation includes N=756 for placebo and N=762 for baricitinib
c. Number of events does not meet optimal information size
d. 95% CI cannot exclude no harm.
e. Non-comparative serious adverse events were reported in the RECOVERY 2022 trial (baricitinib N=4,148): 13 total (5 serious infections, 3 bowel perforations, 2 pulmonary embolisms, 1 each of ischemic colitis, elevated transaminases and seizure)

References
Table 21. GRADE evidence profile, Recommendation 20

**Question:** Baricitinib compared to no baricitinib for critically ill (OS-7) patients with COVID-19 pneumonia requiring invasive mechanical ventilation

**Last reviewed and updated 4/29/2022**

<table>
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<th>Table 21. GRADE evidence profile, Recommendation 20</th>
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<td>№ of studies</td>
<td>Study design</td>
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<td>randomized trials</td>
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<td>Invasive mechanical ventilation free days (follow-up: 60 days)</td>
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<tr>
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<td>randomized trials</td>
</tr>
<tr>
<td>Days of hospitalization (follow-up: 60 days)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
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<tr>
<td>Serious adverse events (follow-up: 28 days)</td>
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</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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- **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

Tables and Figures

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Inconsistency: Unexplained heterogeneity across study findings</td>
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<tr>
<td>Indirectness: Applicability or generalizability to the research question</td>
</tr>
<tr>
<td>Imprecision: The confidence in the estimate of an effect to support a particular decision</td>
</tr>
<tr>
<td>Publication bias: Selective publication of studies</td>
</tr>
</tbody>
</table>

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; MD: Mean difference; RR: Risk ratio

Explanations

a. Few number of events, does not meet optimal information size
b. Pooled mortality event data RR: 0.73 (95% CI: 0.50, 1.06) cannot exclude no meaningful benefit and therefore suggests fragility when compared with the HR.
c. 95% CI includes both the possibility of benefit and risk of harm
d. Adjusted for age (<65, ≥65) and region (U.S., rest of the world)
e. 95% CI cannot exclude no benefit

Reference

### Table 22. GRADE evidence profile, Recommendation 21

**Question:** Baricitinib with remdesivir compared to remdesivir for hospitalized patients with COVID-19

**Last updated 5/16/2021; last reviewed 10/11/2021**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (follow-up: 28 days)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (^1) randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious (^a)</td>
<td>none</td>
</tr>
<tr>
<td><strong>Clinical recovery - hospitalized requiring supplemental O(_2)/receiving noninvasive ventilation or high-flow O(_2) (ordinal 5+6) (assessed with: Ordinal scale &lt;4)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1 (^1) randomized trials</td>
<td>serious (^b)</td>
<td>not serious</td>
<td>not serious</td>
<td>serious (^c)</td>
</tr>
<tr>
<td><strong>Clinical recovery - receiving noninvasive ventilation or high-flow O(_2), invasive mechanical ventilation or ECMO (ordinal 6+7; stratified) (assessed with: Ordinal scale &lt;4)</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1 (^1) randomized trials</td>
<td>not serious (^d)</td>
<td>not serious</td>
<td>not serious</td>
<td>serious (^e)</td>
</tr>
<tr>
<td><strong>New use of mechanical ventilation or ECMO (follow-up: 29 days)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 (^1) randomized trials</td>
<td>serious (^f)</td>
<td>not serious</td>
<td>not serious</td>
<td>serious (^g)</td>
</tr>
<tr>
<td><strong>Serious adverse events (follow-up: 28 days)</strong></td>
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<td></td>
</tr>
<tr>
<td>1 (^1) randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious (^g)</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 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.

<table>
<thead>
<tr>
<th>CI</th>
<th>Confidence interval; RR: Risk ratio; HR: Hazard Ratio; OR: Odds ratio; RDV: Remdesivir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Explanations</strong></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td>95% CI includes substantial benefits as well as substantial harms</td>
</tr>
<tr>
<td>b.</td>
<td>Non-stratified subgroup post hoc analysis.</td>
</tr>
<tr>
<td>c.</td>
<td>Lower boundary of the 95% CI crosses our threshold for a meaningful difference.</td>
</tr>
<tr>
<td>d.</td>
<td>Data from table S6. Although described as &quot;analysis as randomized&quot; in this stratum of severe COVID-19 patients, the analysis included moving patient from a baseline of &quot;moderate&quot; to &quot;severe&quot; post hoc (19 in the baricitinib group vs 21 in the placebo group), thus altering the original stratification. However, re-analysis using to original strata data (ordinal scale 6 and 7 from table 2) and 28-day cutoff (as a binary, non-time to event analysis) produce a similar result (RR 1.2, 95% CI 1.005 to 1.43). Not rated down for post hoc analysis concerns.</td>
</tr>
<tr>
<td>e.</td>
<td>95% CI includes substantial benefits as well as no effect</td>
</tr>
<tr>
<td>f.</td>
<td>Not a predefined stratum. Secondary analysis.</td>
</tr>
<tr>
<td>g.</td>
<td>Less than 300 events; concern for fragility</td>
</tr>
<tr>
<td>h.</td>
<td>SAEs in 5 or more participants in any preferred term by treatment group. 6/507 were thought related to study drug in the baricitinib group; 5/509 were thought to be related to the study drug in the placebo group.</td>
</tr>
</tbody>
</table>

### Reference

Table 23. GRADE evidence profile, Recommendation 22
Question: Tofacitinib compared to no tofacitinib for hospitalized patients with COVID-19

New evidence profile developed 8/21/2021

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Death or respiratory failure (follow-up: 28 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Mortality (follow-up: 28 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Progression to mechanical ventilation or ECMO (follow-up: 28 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious adverse events (follow-up: 28 days)</td>
<td>1</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; ECMO: Extracorporeal mechanical oxygenation; RR: Risk ratio

Explanations
a. Small number of events; fragility present.
b. Upper boundary of the 95% CI crosses a threshold of meaningful effect.
c. 95% CI cannot exclude no harm.
d. One DVT was observed in the tofacitinib group vs zero in the placebo group.

Reference
Ivermectin

Evidence profiles

- Ivermectin compared to no ivermectin for patients hospitalized with COVID-19
- Ivermectin compared to no ivermectin for ambulatory persons for management of COVID-19
Table 24. GRADE evidence profile, Recommendation 23

**Question:** Ivermectin compared to no ivermectin for patients hospitalized with COVID-19

*Last reviewed and updated 10/10/2022*

<table>
<thead>
<tr>
<th>Mortality (follow-up: range 14 days to 28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>11 1-11 randomized trials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Need for mechanical ventilation (follow-up: 28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>3 7,8,11 randomized trials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom resolution (follow-up: 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>1 12 randomized trials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Viral clearance at day 7 (RCT) (follow-up: range 7 days to 29 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>6 4,5,8,10,13,14 randomized trials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious adverse events (follow-up: 28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>6 2,4,7,8,9,11 randomized trials</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
**IDSA Guideline on the Treatment and Management of COVID-19**

**Tables and Figures**

**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 has not been peer reviewed or published.

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

**Explanations**

a. Hashim 2021 allocated patients based on odd/even days of recruitment.

b. Substantial heterogeneity observed (I²=68%) and introduced by Elshafie 2022 in which mortality events were reported at day 14 instead of 28 days.

c. The 95% CI cannot exclude no meaningful effect. Few events reported do not meet the optimal information size and suggest fragility of the estimate

d. Open label trial may lead to bias with measurement of subjective outcomes.

e. Podder 2020 assigns participants based on odd or even registration numbers, also, 20 patients were excluded following randomization without sensitivity analysis to explore imbalance across treatment arms.

f. Some heterogeneity observed (I²=53%). Possibly explained by the longer duration of treatment (5 days compared to 1 day) in Ahmed 2021.

g. Viral clearance is a surrogate for clinical improvement, such as hospitalization, need for ICU care and mechanical ventilation.

**References**


Version 10.1.1
**Table 25.** GRADE evidence profile, Recommendation 24  

**Question:** Ivermectin compared to no ivermectin for ambulatory persons for management of COVID-19  

*Last reviewed and updated 10/10/2022*

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Other considerations</td>
<td>ivermectin</td>
<td>no ivermectin</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
<td>Certainty</td>
<td>Importance</td>
</tr>
<tr>
<td>Mortality</td>
<td>14 1-14</td>
<td>randomized trials</td>
<td>not serious  (^a)</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>29/3580 (0.8%)</td>
<td>37/3393 (1.1%)</td>
<td>RR 0.86 (0.53 to 1.40)</td>
<td>2 fewer per 1,000 (from 5 fewer to 4 more)</td>
<td>☻☻☻☻ HIGH</td>
<td>CRITICAL</td>
<td></td>
</tr>
<tr>
<td>Progression to severe disease (assessed with: need for invasive ventilation)</td>
<td>7 1,2,4,5,7,8,12</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious  (^b)</td>
<td>none</td>
<td>31/1505 (2.1%)</td>
<td>43/1375 (3.1%)</td>
<td>RR 0.70 (0.44 to 1.11)</td>
<td>9 fewer per 1,000 (from 18 fewer to 3 more)</td>
<td>☻☻☻ MODERATE</td>
<td>CRITICAL</td>
<td></td>
</tr>
<tr>
<td>Hospitalization (follow-up: 28 days)</td>
<td>7 8,10-15</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious  (^c)</td>
<td>none</td>
<td>134/2714 (4.9%)</td>
<td>141/2517 (5.6%)</td>
<td>RR 0.88 (0.71 to 1.11)</td>
<td>7 fewer per 1,000 (from 16 fewer to 6 more)</td>
<td>☻☻☻ MODERATE</td>
<td>CRITICAL</td>
<td></td>
</tr>
<tr>
<td>Viral clearance at day 7 (RCT) (follow-up: range 6 days to 29 days)</td>
<td>6 2,4,8,13,15</td>
<td>randomized trials</td>
<td>not serious</td>
<td>serious  (^d,e)</td>
<td>very serious  (^e)</td>
<td>none</td>
<td>178/574 (31.0%)</td>
<td>193/281 (68.7%)</td>
<td>RR 1.01 (0.78 to 1.31)</td>
<td>7 more per 1,000 (from 151 fewer to 213 more)</td>
<td>☻☻☻☺☺☺ VERY LOW</td>
<td>IMPORTANT</td>
<td></td>
</tr>
<tr>
<td>Time to recovery (assessed with: days)</td>
<td>4 1,5,6,12</td>
<td>randomized trials</td>
<td>very serious  (^f)</td>
<td>not serious  (^b)</td>
<td>not serious</td>
<td>none</td>
<td>709</td>
<td>576</td>
<td>-</td>
<td>MD 2.99 days fewer (4.76 fewer to 1.22 fewer)</td>
<td>☻☻☻☺☺☺ VERY LOW</td>
<td>IMPORTANT</td>
<td></td>
</tr>
</tbody>
</table>

Serious adverse events (respiratory failure, sepsis, multiorgan failure, etc.)
### Tables and Figures

<table>
<thead>
<tr>
<th>7 2.3.5.8.10.11.16</th>
<th>randomized trials</th>
<th>not serious</th>
<th>not serious</th>
<th>not serious</th>
<th>serious</th>
<th>none</th>
<th>31/1973 (1.6%)</th>
<th>40/1933 (2.1%)</th>
<th>RR 0.81 (0.51 to 1.30)</th>
<th>4 fewer per 1,000 (from 10 fewer to 6 more)</th>
<th>●●●○</th>
<th>MODERATE</th>
<th>CRITICAL</th>
</tr>
</thead>
</table>

**GRADE Working Group grades of evidence**

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- **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 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 has not been peer reviewed or published.

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

**Explanations**

a. Concerns with unmeasured and residual confounding. Hashim 2021 allocated patients based on odd/even days of recruitment.

b. The 95% CI cannot exclude no benefit from treatment.

c. The 95% CI includes the potential for both appreciable benefit as well as the potential for harm. Few events reported do not meet the optimal information size and suggest fragility of the estimate.

d. Viral clearance is a surrogate for clinical improvement, such as hospitalization, need for ICU care and mechanical ventilation.

e. Ravikirti 2021 reported viral clearance at day 6.

f. Open label trial may lead to bias with measurement of subjective outcomes.

g. High heterogeneity I^2=90% introduced by Hashim 2021.

h. Ivermectin was combined with doxycycline.

i. The binary endpoint of time to recovery from the ACTIV-6 trial could not be combined with pooled continuous analysis of days to recovery; however, did not show a reduction with a HR: 1.09 (0.98, 1.22).

j. The 95% CI cannot exclude the potential of increased SAEs in the treatment arm. Few events suggest fragility in the estimate.

**References**


3. Bukhari SKHS, Asghar A, Perveen N, et al. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease. medRxiv 2021: Available at: [https://doi.org/10.1101/2021.01.05.21249310](https://doi.org/10.1101/2021.01.05.21249310) [Preprint 5 February 2021].


Fluvoxamine

Evidence profiles

- Fluvoxamine compared to no fluvoxamine for ambulatory patients with COVID-19
### Table 26. GRADE evidence profile compared to no fluvoxamine for ambulatory patients with COVID-19

**Question:** Fluvoxamine compared to no fluvoxamine for ambulatory patients with COVID-19

*New evidence profile developed 10/22/2021; last updated 11/8/2021*

#### Certainty assessment

<table>
<thead>
<tr>
<th>Nr of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nr of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>fluvoxamine</td>
<td>no fluvoxamine</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
<tr>
<td>Mortality (follow up: 28 days) *</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2¹ 2²</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious b</td>
<td>none</td>
<td>17/821 (2.1%)</td>
<td>25/828 (3.0%)</td>
<td>RR 0.69 (0.38 to 1.27)</td>
<td>9 fewer per 1,000 (from 19 fewer to 8 more)</td>
</tr>
<tr>
<td>Hospitalization, emergency room visits (&gt;6 hours), or oxygen saturation &lt;92% (follow up: 28 days) *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2¹ 2²</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>79/821 (9.6%)</td>
<td>125/828 (15.1%)</td>
<td>RR 0.64 (0.50 to 0.84)</td>
<td>54 fewer per 1,000 (from 75 fewer to 24 fewer)</td>
</tr>
<tr>
<td>Hospitalization for COVID-19 (follow up: 28 days) *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2¹ 2²</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious b</td>
<td>none</td>
<td>76/821 (9.3%)</td>
<td>103/828 (12.4%)</td>
<td>RR 0.75 (0.57 to 0.99)</td>
<td>31 fewer per 1,000 (from 53 fewer to 1 fewer)</td>
</tr>
<tr>
<td>Viral clearance (follow up: 7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1¹ 2²</td>
<td>randomized trials</td>
<td>serious d</td>
<td>not serious</td>
<td>serious e</td>
<td>very serious b</td>
<td>none</td>
<td>40/207 (19.3%)</td>
<td>58/221 (26.2%)</td>
<td>RR 0.74 (0.52 to 1.05)</td>
<td>68 fewer per 1,000 (from 126 fewer to 13 more)</td>
</tr>
<tr>
<td>Serious adverse events *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2¹ 2²</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious f</td>
<td>none</td>
<td>60/821 (7.3%)</td>
<td>75/828 (9.1%)</td>
<td>RR 0.81 (0.59 to 1.12)</td>
<td>17 fewer per 1,000 (from 37 fewer to 11 more)</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
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#### 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; MD: Mean difference

Explanations
a. Lenze et al had a 15-day follow-up period; Reis et al had a 28-day follow-up period; Serious adverse events for Reis et al included only the non-mortal grade 4 and grade 3 treatment emergent adverse events.
b. 95% CI includes both the potential for benefit and the risk of harms; few events suggest fragility of the estimate.
c. Hospitalization, emergency room visits are surrogate marker for clinical deterioration leading to ICU care, ventilation and mortality. In addition, best supportive care may have been substantially different in Brazil at that time compared to the U.S. health system.
d. Data available for approximately 1/3 of study population per treatment group.
e. Viral clearance is a surrogate for clinical improvement, such as hospitalization, need for ICU care, and mechanical ventilation.
f. 95% CI cannot exclude the possibility of meaningful harm.

References
Nirmatrelvir/ritonavir

Evidence profiles

- Nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

FDA Emergency Use Authorization criteria

- FDA EUA criteria for the use of nirmatrelvir/ritonavir co-packaged as Paxlovid™

Contraindications

- Nirmatrelvir/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions
- Nirmatrelvir/ritonavir is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance
Table 27. GRADE evidence profile, Recommendation 26

**Question:** Nirmatrelvir/ritonavir compared to no nirmatrelvir/ritonavir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

*New evidence profile developed 12/23/2021; last updated 2/3/2022*

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>All-cause mortality (follow-up: 28 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>serious a</td>
<td>not serious</td>
</tr>
<tr>
<td>COVID-19-related hospitalizations (follow-up: 28 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>serious a</td>
<td>not serious</td>
</tr>
<tr>
<td>COVID-19-related hospitalization or all-cause death (follow-up: 28 days)</td>
<td>1</td>
<td>randomized trials</td>
<td>serious a</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious adverse events - not reported</td>
<td></td>
<td></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.
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- **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 are derived from evidence that has not been peer reviewed or published.*

CI: Confidence interval; RR: Risk ratio

**Explanations**
a. Evidence profile based on information reported in FDA EUA and due to limited available study details, unable to exclude potential risks of bias. Concerns about selective outcome reporting as hospitalization or death from any cause and all-cause mortality are reported out of 10 outcome measures identified in the trial protocol, including SAEs and adverse events.

b. The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I.

c. Small number of events; fragility present

d. Recalculated due to zero events in the intervention arm.

e. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.

Reference

Figure 2. FDA EUA criteria for the use of nirmatrelvir/ritonavir co-packaged as Paxlovid™

| Paxlovid is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. |

Reference


Figure 3. Nirmatrelvir/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: ilarasidone, pimozide
- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylerygononine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- Vasopressin receptor antagonists: tolvapta

*Please check drug interactions before initiating nirmatrelvir/ritonavir as the table above does not list all therapeutic agents or classes with potential interactions; see Liverpool COVID-19 Interactions website.

Reference

**Figure 4.** Nirmatrelvir/ritonavir is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.  

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Antimycobacterials: rifampin
- Herbal products: St. John’s Wort (*Hypericum perforatum*)

**Reference**

Molnupiravir

Evidence profiles

- Molnupiravir compared to no molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

FDA Emergency Use Authorization criteria

- FDA EUA criteria for the use of molnupiravir
### Table 28. GRADE evidence profile, Recommendation 27

**Question:** Molnupiravir compared to no molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

*New evidence profile developed 12/30/2021*

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COVID-19-related mortality (follow-up: range 28 days to 29 days)</strong></td>
<td>2</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious, b, c, d</td>
<td>1/764 (0.1%)</td>
<td>RR 0.11 (0.01 to 0.86)</td>
<td>11 fewer per 1,000 (from 12 fewer to 2 fewer)</td>
</tr>
<tr>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious, c, f</td>
<td>none</td>
<td>45/709 (6.3%)</td>
<td>RR 0.68 (0.48 to 1.00)</td>
<td>29 fewer per 1,000 (from 48 fewer to 0 fewer)</td>
</tr>
<tr>
<td><strong>Hospitalization or death (all-cause) (follow-up: 29 days)</strong></td>
<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious, b, c, f</td>
<td>none</td>
<td>HR 0.69 (0.48 to 1.01)</td>
<td>29 fewer per 1,000 (from 49 fewer to 1 more)</td>
</tr>
<tr>
<td><strong>Serious adverse events (follow-up: range 28 days to 29 days)</strong></td>
<td>2</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious, f, g</td>
<td>none</td>
<td>RR 0.43 (0.17 to 1.11)</td>
<td>10 fewer per 1,000 (from 15 fewer to 2 more)</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 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 are derived from evidence that has not been peer reviewed or published.

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

Explanations
a. In Bernal 2021, after day 29, one additional death resulting from adverse events occurred in the molnupiravir group and three additional deaths occurred in the placebo group. In Fischer 2021, at day 31, one additional death resulting from hypoxia occurred in the placebo group.
b. Small number of events; fragility present.
c. 95% CI cannot exclude no meaningful benefit.
d. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.
e. All 10 patients reported as died at day 29 had been hospitalized.
f. Small number of events.
g. 95% CI cannot exclude the possibility of harms.

References
**Figure 5.** FDA EUA criteria for the use of molnupiravir

| Molnupiravir may only be used for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high-risk for progression to severe COVID, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. |

**Reference**

Colchicine

Evidence profiles

- Colchicine compared to no colchicine for hospitalized patients with COVID-19
- Colchicine compared to no colchicine for ambulatory persons with mild-to-moderate COVID-19
Table 29. GRADE evidence profile, Recommendation 28
Question: Colchicine compared to no colchicine for hospitalized patients with COVID-19

Last reviewed and updated 6/13/2022

<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>
</tbody>
</table>

Mortality

10

| 1-10 randomized trials | not serious | not serious | not serious | serious a | none | 1335/6684 (20.0%) | 1385/6810 (20.3%) | RR 0.99 (0.92 to 1.06) | 2 fewer per 1,000 (from 16 fewer to 12 more) | ✭✭✭ MODERATE | CRITICAL |

Mechanical ventilation

5

| 4-8 randomized trials | not serious b | not serious | not serious | not serious | none | 652/6242 (10.4%) | 651/6370 (10.2%) | RR 1.02 (0.90 to 1.16) | 2 more per 1,000 (from 10 fewer to 16 more) | ✭✭✭✭ HIGH | CRITICAL |

Length of hospital stay

4

| 1-3 randomized trials | serious c | serious d | not serious | serious e,e | none | 134 | 132 | - | MD 1.77 days fewer (3.69 fewer to 0.15 more) | ✭✭✭✭ VERY LOW | CRITICAL |

Adverse events

3

| 8-10 randomized trials | serious c | not serious | not serious | serious e,f | none | 41/148 (27.7%) | 20/151 (13.2%) | RR 2.04 (1.07 to 3.91) | 138 more per 1,000 (from 9 more to 385 more) | ✭✭✭ LOW | 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
IDSA Guideline on the Treatment and Management of COVID-19

Tables and Figures

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. 95% CI cannot exclude the potential for both meaningful benefit or harm.
b. Largest trial was not blinded.
c. Subjectively measured outcome with >50% of studies in analysis with unclear or unreported methods for randomization and lack of blinding.
d. High I² (97%). One study had an imbalance of patients receiving dexamethasone (23% vs 45% in intervention vs placebo arm) possibly contributing to shorter duration of hospitalization in placebo arm.
e. Few events suggest fragility of the estimate.
f. 95% CI cannot exclude the potential for no meaningful harm.

References

Table 30. GRADE evidence profile, Recommendation 29

**Question:** Colchicine compared to no colchicine for ambulatory persons with mild-to-moderate COVID-19

*Last reviewed and updated 6/13/2022*

<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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>3&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>randomized trials</td>
<td>not serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>2&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>randomized trials</td>
<td>not serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>2&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1&lt;sup&gt;1&lt;/sup&gt;</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 has not been peer reviewed or published.

CI: Confidence interval; RR: Risk ratio

Explanations
a. Potential bias due to unclear or unreported details of randomization or deviations from intended interventions; however, low risk of bias for these domains within the study carrying the largest weight in the analysis and findings are not inconsistent.
b. Few events suggests fragility of the estimate.
c. Hospital admission is an intermediary outcome for morbidity, ICU admission, and need for ventilation. Not rated down.
d. 95% CI cannot exclude no meaningful benefit.
e. 95% CI cannot exclude no meaningful difference.

References
How to approach a patient when considering pharmacologic treatments for COVID-19

- Assessment of clinical severity of COVID-19 to target treatments
- Precautions with therapeutic agents used in treating COVID-19
- COVID-19 therapies by disease severity and care location
**Table 31.** Assessment of clinical severity of COVID-19 to target treatments

<table>
<thead>
<tr>
<th>Severity of COVID-19</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-to-moderate COVID-19 (SpO₂ ≥94% on room air and not needing supplemental oxygen) with risk factors for progression to severe disease, hospitalization or death (^a)</td>
<td></td>
</tr>
<tr>
<td>Severe but not critical COVID-19 (SpO₂&lt;94% on room air or needing low-flow supplemental oxygen)</td>
<td></td>
</tr>
<tr>
<td>Critical COVID-19 needing high-flow oxygen/ or non-invasive ventilation</td>
<td></td>
</tr>
<tr>
<td>Critical COVID-19 needing mechanical ventilation or ECMO</td>
<td></td>
</tr>
</tbody>
</table>

**ECMO:** Extracorporeal membrane oxygenation; **SpO₂:** Oxygen saturation

\(^a\) A few of the risk factors are: age >60 years, BMI >25, diabetes, hypertension, cardiovascular disease, chronic lung disease, cancer, or immunocompromised patients. Risk factors for progression are changing as the epidemic evolves with new variants, vaccination, and previous infection rates.
### Table 32. Precautions with therapeutic agents used in treating COVID-19

<table>
<thead>
<tr>
<th>Characteristic or concern</th>
<th>Therapeutic agents</th>
</tr>
</thead>
</table>
| Reduced eGFR/ increased creatinine (specific cut-offs to be mentioned for each agent) | - Remdesivir- Use with caution when CrCl <30 mL/min  
- Baricitinib- dose adjustment when CrCl <60 mL/min; not recommended for eGFR, 15 mL/min  
- Tofacitinib- dose adjustment when CrCl <50 mL/min  
- Nirmatrelvir/ritonavir- dose adjustment when eGFR <60 mL/min; not recommended for eGFR <30 mL/min |
| Increased AST or ALT (specific cut-offs to be mentioned for each agent) | - Baricitinib- discontinue if ALT or AST increases due to treatment  
- Remdesivir- consider discontinuation if ALT/AST increases to >10x the upper limit of normal  
- Tofacitinib- reduce dose for moderate hepatic impairment  
- Tocilizumab- may cause hepatic injury  
- Sarilumab- warning to avoid when ALT/AST are >1.5x ULN; discontinue if ALT/AST become 5x ULN during therapy |
| Cytopenias (specific cut-offs to be mentioned for each agent) | - Tofacitinib- warning to avoid when lymphocytes <500 cells/mm³, neutrophils <1000 cells/mm³, or hemoglobin <9 g/dL  
- Baricitinib- warning to avoid when lymphocytes <500 cells/mm³, neutrophils <1000 cells/mm³, or hemoglobin <8 g/dL  
- Tocilizumab- associated with neutropenia and thrombocytopenia; warning to avoid for chronic use when ANC <2000 cells/mm³ or platelets <100,000 per mm³  
- Sarilumab- associated with neutropenia and thrombocytopenia; warning to avoid for chronic use when ANC <2000 cells/mm³ or platelets <150,000 per mm³ |
<p>| Anti-rejection medications | - Nirmatrelvir/ritonavir significantly increases concentrations of tacrolimus, cyclosporine, and sirolimus. Dose modification or temporary discontinuation of these agents are required during concomitant use. |</p>
<table>
<thead>
<tr>
<th>Characteristic or concern</th>
<th>Therapeutic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (pediatric and adolescent) (^b)</td>
<td>• Molnupiravir is suggested for patients &gt;18 years</td>
</tr>
<tr>
<td></td>
<td>• Tocilizumab is suggested for patients &gt;2 years</td>
</tr>
<tr>
<td></td>
<td>• Sarilumab is suggested for patients &gt;18 years</td>
</tr>
<tr>
<td></td>
<td>• Baricitinib is suggested for patients &gt;2 years</td>
</tr>
<tr>
<td></td>
<td>• Tofacitinib is suggested for patients &gt;2 years</td>
</tr>
<tr>
<td></td>
<td>• Neutralizing antibodies are suggested for patients &gt;12 years</td>
</tr>
<tr>
<td></td>
<td>• Nirmatrelvir/ritonavir is suggested for patients &gt;12 years</td>
</tr>
<tr>
<td></td>
<td>• Remdesivir is indicated for all ages</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone is indicated for all ages</td>
</tr>
</tbody>
</table>

| Reproductive concerns and pregnancy                    | • Molnupiravir is not recommended during pregnancy                                   |
|                                                       | • Females: Advise individuals of childbearing potential to use a reliable method of contraception for the duration of treatment and for 4 days after the last dose of molnupiravir |
|                                                       | • Males: Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception during treatment and for at least 3 months after the last dose of molnupiravir |

**ALT:** Alanine transaminase; **ANC:** Absolute neutrophil count; **AST:** Aspartate transaminase; **CrCl:** Creatinine clearance; **eGFR:** Estimated glomerular filtration rate; **ULN:** Upper limit of normal

- **a.** Warnings come from chronic use of these medications for rheumatological disease. Patients with COVID-19 may have cytopenias, particularly lymphocytopenia, due to the viral infection. Using these agents in that situation may be indicated.
- **b.** Most pediatric data is derived from adult patients or other indications for these drugs.
Table 33. COVID-19 therapies by disease severity and care location

<table>
<thead>
<tr>
<th>Care location and COVID-19 severity</th>
<th>Pharmacologic treatments available in the United States</th>
</tr>
</thead>
</table>
| Ambulatory mild-to-moderate disease (not hypoxemic) with high risk for progression to severe disease, hospitalization or death (see individual drug section for specific considerations for each of these agents) | • Nirmatrelvir/ritonavir X 5 days (oral)  
• Remdesivir x 3 days (intravenous)  
• Anti-SARS-CoV-2 monoclonal antibodies \(^a\)  
• If other treatment options are not available then consider Molnupiravir x 5 days (oral) or, if immunocompromised, high-titer convalescent plasma with activity against circulating variant (intravenous).  
• Systemic steroids have no demonstrated benefit and may harm.  
• No benefit demonstrated for hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin. |
| Can be considered in patients with mild-moderate COVID-19 hospitalized for other reasons |  |
| Hospitalized for mild-to-moderate COVID-19 (not hypoxemic) | • If at high risk for progression and within 7 days of symptom onset, remdesivir x 3 days.  
• Systemic steroids have no demonstrated benefit and may harm.  
• No benefit demonstrated in RCTs for convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin. |
| Hospitalized for severe, but not critical COVID-19 (hypoxemic needing low flow supplemental oxygen) | • Corticosteroids (dexamethasone 6 mg/d x 10 days or until discharge or an equivalent dose of another agent).  
• Remdesivir x 5 days  
• Tocilizumab or Sarilumab in progressive disease with elevated inflammatory makers.  
  or  
• Baricitinib or tofacitinib in patients with elevated inflammatory markers.  
• No benefit demonstrated in RCTs for convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin. |
| Hospitalized for critically ill COVID-19, needing non-invasive ventilation or Hi flow oxygen | Corticosteroids (dexamethasone 6 mg/d x 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone).  
• Tocilizumab or Sarilumab in patients with elevated inflammatory makers |
<table>
<thead>
<tr>
<th>Care location and COVID-19 severity</th>
<th>Pharmacologic treatments available in the United States</th>
</tr>
</thead>
</table>
| • Baricitinib or tofacitinib in patients with elevated inflammatory markers  
• No benefit demonstrated in RCTs for remdesivir, convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin. | |
| Hospitalized for critically ill COVID-19, needing invasive mechanical ventilation or ECMO | • Corticosteroids (dexamethasone 6 mg/d x 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone).  
• Tocilizumab or sarilumab in patients with elevated inflammatory markers  
• Baricitinib or tofacitinib in patients with elevated inflammatory markers  
• No benefit demonstrated in RCTs for remdesivir, convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin. |

ECMO: Extracorporeal membrane oxygenation; RCTs: Randomized controlled trials

a. Neutralizing antibodies that are active against prevalent variants should be utilized. For example, at present (04/2022) bebtelovimab has *in vitro* activity against Omicron BA.2 subvariant and should be utilized, but casirivimab/imdevimab, bamlanivimab/etesevimab and sotrovimab do not have reliable activity against circulating omicron BA.2 variant and should be avoided.
Pediatric considerations for treatment of SARS-CoV-2 infection and multisystem inflammatory syndrome in children

- Case definitions for Multisystem Inflammatory Syndrome in Children (MIS-C) and Paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TC, also called pediatric multisystem inflammatory disorder [PMIS])
Table 34. Case definitions for Multisystem Inflammatory Syndrome in Children (MIS-C) and Paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TC, also called pediatric multisystem inflammatory disorder (PMIS))

<table>
<thead>
<tr>
<th>MIS-C (CDC 2020)¹</th>
<th>PIMS-TS or PMIS (Royal College of Paediatrics and Child Health 2020)²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Includes</strong></td>
<td></td>
</tr>
<tr>
<td>Age &lt;21 years presenting with:</td>
<td>A child presenting with:</td>
</tr>
<tr>
<td>• Fever (&gt;38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours)</td>
<td>• Persistent fever &gt;38.5°C</td>
</tr>
<tr>
<td>• Laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin),</td>
<td>• Laboratory evidence of inflammation (neutrophilia, elevated CRP and lymphopenia)</td>
</tr>
<tr>
<td>• Evidence of clinically severe illness requiring hospitalization, with multisystem (&gt;2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)</td>
<td>• Evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (listed in Appendix of reference)</td>
</tr>
<tr>
<td><strong>Excludes</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with alternative plausible diagnoses</td>
<td>Patients with any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus</td>
</tr>
<tr>
<td><strong>Other criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; OR COVID-19 exposure within the 4 weeks prior to the onset of symptoms</td>
<td>SARS-CoV-2 PCR testing may be positive or negative</td>
</tr>
</tbody>
</table>

References