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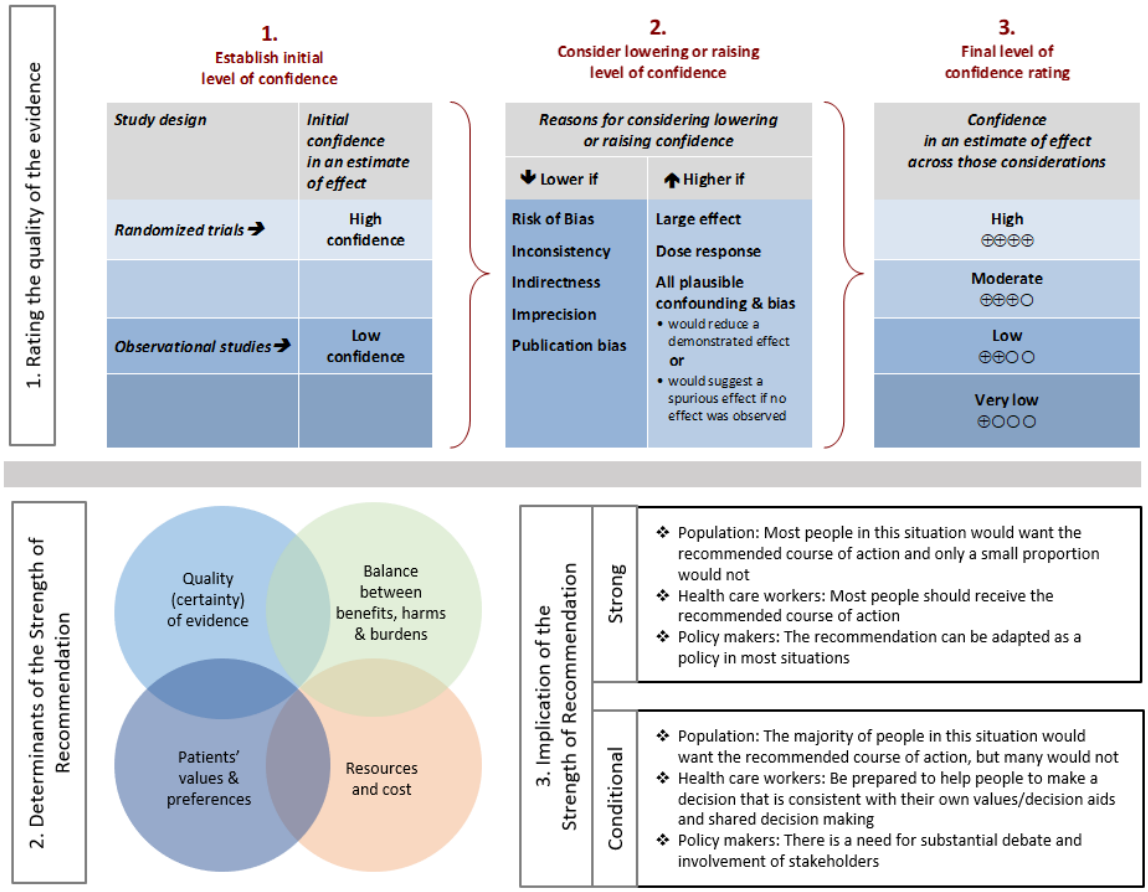
Methods

- 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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxy-chloroquine	no hydroxy-chloroquine	Relative (95% CI)	Absolute (95% CI)		
Mortality (RCTs) (follow up: range 22 days to 49 days)												
5 [1-5]	randomized trials	not serious [a]	not serious	not serious [b]	serious [c]	none	561/2976 (18.9%)	908/4532 (20.0%)	**RR 1.08** (0.99 to 1.19)	**16 more per 1,000** (from 2 fewer to 38 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical status (assessed with: 7-point scale; higher signifies worsening severity)												
1 [2]	randomized trials	serious [d]	not serious	not serious	serious [e]	none	159	173	-	median **1.21 higher** (0.69 higher to 2.11 higher)	⨁⨁◯◯ LOW	CRITICAL
Progression to invasive mechanical ventilation												
2 [1,3]	randomized trials	serious [f]	not serious	not serious	serious [c]	none	193/2162 (8.9%)	281/3447 (8.2%)	**RR 1.10** (0.92 to 1.31)	**8 more per 1,000** (from 7 fewer to 25 more)	⨁⨁◯◯ LOW	CRITICAL
Arrhythmias												
1 [6]	observational studies	very serious [g]	not serious	not serious	very serious [e,h]	none	44/271 (16.2%)	23/221 (10.4%)	**RR 1.56** (0.97 to 2.50)	**58 more per 1,000** (from 3 fewer to 156 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events, any												
4 [2,7-9]	randomized trials	serious [i]	not serious	not serious	serious [e]	none	94/315 (29.8%) [j]	18/176 (10.2%) [k]	**RR 2.36** (1.49 to 3.75)	**139 more per 1,000** (from 50 more to 281 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxy-chloroquine	no hydroxy-chloroquine	Relative (95% CI)	Absolute (95% CI)		
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)												
1 [4]	randomized trials	not serious	not serious	not serious	very serious [e]	none	14/242 (5.8%)	11/237 (4.6%)	**OR 1.26** (0.56 to 2.84) [l]	**11 more per 1,000** (from 20 fewer to 75 more)	⨁⨁◯◯ LOW	CRITICAL
QT prolongation (RCTs)												
1 [2]	randomized trials	not serious	not serious	not serious	very serious [h]	none	13/89 (14.6%)	1/58 (1.7%)	**RR 8.47** (1.14 to 63.03)	**129 more per 1,000** (from 2 more to 1,000 more)	⨁⨁◯◯ LOW	IMPORTANT
QT prolongation (NRS)												
2 [6,10]	observational studies	very serious [g,m]	not serious	not serious	serious [h]	none	46/355 (13.0%)	13/311 (4.2%)	**RR 2.89** (1.62 to 5.16)	**79 more per 1,000** (from 26 more to 174 more)	⨁◯◯◯ VERY 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

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 Abidiol 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. Three AEs reported in two patients include: AST elevation, creatinine elevation and anemia
l. aOR: age, sex, baseline COVID Outcome Scale category, baseline Sequential Organ Failure Assessment score, and duration of acute respiratory infection symptoms prior to randomization
m. Mahevas 2020 does not report on AEs in the comparator arm.

References

1. RECOVERY Collaborative Group, Horby P, Mafham M, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med **2020**; 383(21): 2030-40.
2. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med **2020**; 383: 2041-52.
3. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.
4. Self WH, Semler MW, Leither L, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: A randomized clinical trial. JAMA **2020**; 324(21): 2165-76.
5. Ulrich RJ, Troxel AB, Carmody E, et al. Treating COVID-19 With Hydroxychloroquine (TEACH): A Multicenter, Double-Blind Randomized Controlled Trial in Hospitalized Patients Open Forum Infect Dis **2020**; 7(10): ofaa446.
6. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. JAMA **2020**; 323(4): 2493:502.
7. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Journal of Zhejiang University (Medical Sciences) **2020**; 49(2): 215-9.
8. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv **2020**; Available at: https://doi.org/10.1101/2020.03.22.20040758 [Preprint 10 April 2020].
9. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ **2020**; 369: m1849.
10. Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv **2020**; Available at: https://doi.org/10.1101/2020.04.10.20060699 [Preprint 14 April 2020].

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxy-chloroquine	no hydroxy-chloroquine	Relative (95% CI)	Absolute (95% CI)		
Mortality (RCTs) (follow-up: range 22 days to 49 days)												
1 [1]	randomized trials	not serious [a]	not serious	not serious [b]	very serious [c,d]	none	5/172 (2.9%)	6/173 (3.5%)	**HR 0.64** (0.18 to 2.21)	**12 fewer per 1,000** (from 28 fewer to 40 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality (NRS)												
3 [2-4]	observational studies	very serious [e]	not serious	not serious	serious [d]	none	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) [2-4]				⨁◯◯◯ VERY LOW	CRITICAL
Clinical status (assessed with: 7-point scale, higher values represent worse clinical outcomes)												
1 [1]	randomized trials	serious [f]	not serious	not serious [b]	serious [d,g]	none	172	173	-	MD **0.99 higher** (0.57 higher to 1.73 higher)	⨁⨁◯◯ LOW	CRITICAL
Virologic failure (follow-up: range 5 days to 6 days; assessed with: PCR test)												
2 [5-7]	observational studies	very serious [h]	serious [i]	serious [j]	serious [c]	none	29/71 (40.8%) [k]	12/12 (100.0%) [l]	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
QT prolongation (RCTs)												
1 [1]	randomized trials	not serious	not serious	serious [m,n]	serious [c]	none	17/116 (14.7%)	1/58 (1.7%)	**RR 8.50** (1.16 to 62.31)	**129 more per 1,000** (from 3 more to 1,000 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxy-chloroquine	no hydroxy-chloroquine	Relative (95% CI)	Absolute (95% CI)		
QT prolongation (NRS)												
2 [7,8]	observational studies	very serious [h]	not serious	serious [n]	serious [c]	none	10/95 (10.5%) [n]	-	-	-	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events												
1 [1]	randomized trials	serious [f]	not serious	not serious [o]	serious [c,d]	none	5/239 (2.1%)	0/50 (0.0%)	**RR 2.34** (0.13 to 41.61)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

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

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

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

CI: Confidence interval; **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%)

l. 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.
m. Indirect measure of arrhythmia-specific mortality.
n. 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.
o. Molina 2020: 1/11 leading to treatment discontinuation; Chorin 2020: 9/84 with significant QTc prolongation of more than 500 ms.
p. Cavalcanti 2020 serious adverse events included pulmonary embolism, Qtc prolongation, myocardial infarction, abdominal-wall hemorrhage.

References

1. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med **2020**; 383: 2041-52.
2. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. JAMA **2020**; 323(4): 2493:502.
3. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med **2020**; 1(1): 114-27.e3.
4. Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients-An Observational Study. PloS One **2020**; 15(8): e0237693.
5. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents **2020**: 56(1): 105949.
6. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis **2020**; 34: 101663.
7. Molina JM, Delaugerre C, Goff J, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Médecine et Maladies Infectieuses **2020**; 50(4): 384.
8. Chorin E, Dai M, Shulman E, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv **2020**; Available at: https://doi.org/10.1101/2020.04.02.20047050 [Preprint 3 April 2020].

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxy-chloroquine	no hydroxy-chloroquine	Relative (95% CI)	Absolute (95% CI)		
Symptomatic SARS-CoV-2 infection (follow-up: 14 days) [a]												
3 [1,2,3]	randomized trials	not serious	not serious	not serious	serious [b]	none	166/1883 (8.8%)	177/1941 (9.1%)	**RR 0.95** (0.77 to 1.16)	**5 fewer per 1,000** (from 21 fewer to 15 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalization (follow-up: 14 days)												
3 [1,2,3]	randomized trials	not serious	not serious	not serious	very serious [b]	none	13/2018 (0.6%)	14/2129 (0.7%)	**RR 1.00** (0.47 to 2.12)	**0 fewer per 1,000** (from 3 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality (follow-up: 14 days)												
3 [1,2,3]	randomized trials	not serious	not serious	not serious	very serious [b]	none	5/2018 (0.2%)	12/2129 (0.6%)	**RR 0.45** (0.16 to 1.28)	**3 fewer per 1,000** (from 5 fewer to 2 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow-up: 14 days)												
3 [1,2,3]	randomized trials	not serious	not serious	not serious	very serious [b]	none	16/2018 (0.8%)	19/2129 (0.9%)	**RR 0.91** (0.47 to 1.76)	**1 fewer per 1,000** (from 5 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL

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

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

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

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

Explanations

a. 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

1. Barnabas RV, Brown ER, Bershteyn A, et al. Hydroxychloroquine as Postexposure Prophylaxis to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 Infection : A Randomized Trial. Ann Intern Med **2021**; 174(3): 344-52.
2. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med **2020**; 383(6): 517-25.
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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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prophylactic lopinavir/ ritonavir	no prophylactic lopinavir/ ritonavir	Relative (95% CI)	Absolute (95% CI)		
Symptomatic SARS-COV-2 infection (COVID-19) regardless of baseline PCR/serology (follow-up: 21 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	35/209 (16.7%)	13/109 (11.9%)	**HR 0.60** (0.29 to 1.26) [b]	**46 fewer per 1,000** (from 83 fewer to 29 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Symptomatic SARS-COV-2 infection (COVID-19), negative PCR and serology at baseline (follow-up: 21 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	8/159 (5.0%)	7/90 (7.8%)	**HR 0.59** (0.17 to 2.02)	**31 fewer per 1,000** (from 64 fewer to 73 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse events (follow-up: 29 days)												
1[1]	randomized trials	serious [c]	not serious	not serious	not serious	none	175/207 (84.5%) [d]	33/107 (30.8%)	**RR 2.74** (2.05 to 3.66)	**537 more per 1,000** (from 324 more to 820 more)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
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; **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

1. Labhardt ND, Smit M, Petignat I, et al. Post-exposure Lopinavir-Ritonavir Prophylaxis versus Surveillance for Individuals Exposed to SARS-CoV-2: The COPEP Pragmatic Open-Label, Cluster Randomized Trial. EClinicalMedicine **2021**; 42: 101188.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lopinavir/ ritonavir	no lopinavir/ ritonavir	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 90 days)												
1[1]	randomized trials	not serious	not serious	not serious	very serious [a]	none	2/244 (0.8%)	1/227 (0.4%)	**RR 1.86** (0.17 to 20.40)	**4 more per 1,000** (from 4 fewer to 85 more)	⨁⨁◯◯ LOW	CRITICAL
COVID-19-related hospitalizations (follow-up: 90 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	14/244 (5.7%)	11/227 (4.8%)	**HR 1.16** (0.53 to 2.56)	**8 more per 1,000** (from 22 fewer to 71 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow-up: 90 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	20/232 (8.6%)	12/220 (5.5%)	**RR 1.58** (0.79 to 3.16)	**32 more per 1,000** (from 11 fewer to 118 more)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
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

1. Reis G, Moreira Silva E, Medeiros Silva DC, et al. Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial. JAMA Netw Open **2021**; 4(4): e216468.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lopinavir/ ritonavir	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
3 [1,2,3]	randomized trials	not serious [a]	not serious	not serious	serious [b]	none	538/3111 (17.3%) [c]	938/4896 (19.2%)	**RR 1.00** (0.89 to 1.13)	**0 fewer per 1,000** (from 21 fewer to 25 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Invasive mechanical ventilation (follow up: 28 days)												
2 [1,3]	randomized trials	serious [a,d]	not serious	not serious	serious [b]	none	166/1655 (10.0%)	297/3380 (8.8%)	**RR 1.12** (0.93 to 1.34)	**11 more per 1,000** (from 6 fewer to 30 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events leading to treatment discontinuation												
1 [1]	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	Nearly 14% of lopinavir–ritonavir recipients were unable to complete the full 14-day course of administration. This was due primarily to gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse events, both acute gastritis. Two recipients had self-limited skin eruptions. Such side effects, including the risks of hepatic injury, pancreatitis, more severe cutaneous eruptions, and QT prolongation, and the potential for multiple drug interactions due to CYP3A inhibition, are well documented with this drug combination. The side-effect profile observed in the current trial arouses concern about the use of higher or more prolonged lopinavir–ritonavir dose regimens in efforts to improve outcomes.				⨁◯◯◯ VERY LOW	IMPORTANT
Failure of clinical improvement at 14 days (follow up: 14 days)												
1 [1]	randomized trials	serious [a]	not serious	not serious	very serious [f]	none	54/99 (54.5%)	70/100 (70.0%)	**RR 0.78** (0.62 to 0.97)	**154 fewer per 1,000** (from 266 fewer to 21 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

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

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

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

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

Explanations

a. 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

1. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med **2020**; 382(19): 1787-99.
2. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.
3. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet **2020**; 396(10259): 1345-52.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cortico-steroids	no cortico-steroids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
8 [1]	randomized trials	not serious	not serious	not serious	not serious	none	280/749 (37.4%)	485/1095 (44.3%)	**OR 0.66** (0.54 to 0.82)	**99 fewer per 1,000** (from 143 fewer to 48 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Hospital discharge (follow up: 28 days)												
1 [2]	randomized trials	not serious [a]	not serious	serious [b]	not serious	none	1360/2104 (64.6%)	2639/4321 (61.1%)	**RR 1.11** (1.04 to 1.19)	**67 more per 1,000** (from 24 more to 116 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events												
6 [1]	randomized trials	not serious	not serious	not serious	serious [c]	none	6 trials reported 64 events among 354 patients randomized to corticosteroids and 80 events among 342 patients randomized to standard care (Stern 2020).				⨁⨁⨁◯ MODERATE	CRITICAL

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

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

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

CI: Confidence interval; **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

1. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA **2020**; 324(13): 1330-41.
2. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med **2021**; 384: 693-704.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gluco-corticoids	no gluco-corticoids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1 [1]	randomized trials	not serious [a]	not serious	serious [b]	not serious	none	454/2104 (21.6%)	1065/4321 (24.6%)	**RR 0.83** (0.74 to 0.92)	**42 fewer per 1,000** (from 64 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospital discharge (follow up: 28 days)												
1 [1]	randomized trials	not serious [a]	not serious	serious [b]	not serious	none	1360/2104 (64.6%)	2639/4321 (61.1%)	**RR 1.11** (1.04 to 1.19)	**67 more per 1,000** (from 24 more to 116 more)	⨁⨁⨁◯ MODERATE	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).				-	CRITICAL

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

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

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

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

Explanations

a. 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

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med **2021**; 384: 693-704.

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 patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gluco-corticoids	no gluco-corticoids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	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 [1]	randomized trials	serious [a]	not serious	not serious	serious [c]	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).				-	CRITICAL

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

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

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

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

Explanations

a. 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

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med **2021**; 384: 693-704.

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, Recommendation 10

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	inhaled corticosteroids	no inhaled corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 14 days to 30 days)												
7 [1-7]	randomized trials	not serious [a]	not serious	not serious [b]	serious [c]	none	7/1951 (0.4%)	13/1925 (0.7%)	**RR 0.58** (0.24 to 1.44)	**3 fewer per 1,000** (from 5 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalizations (follow-up: range 14 days to 30 days)												
6 [1-3,5,7,8]	randomized trials	serious [a]	not serious	not serious [d]	serious [c]	none	95/1928 (4.9%)	122/1906 (6.4%)	**RR 0.81** (0.52 to 1.27)	**12 fewer per 1,000** (from 31 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow-up: range 14 days to 30 days)												
5 [1,3-5,7]	randomized trials	not serious [a]	not serious	not serious	serious [c]	none	36/1671 (2.2%)	26/1727 (1.5%)	**RR 1.14** (0.32 to 3.99)	**2 more per 1,000** (from 10 fewer to 45 more)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
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

1. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet **2021**; 398(10303): 843-55.
2. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA Intern Med **2022**; 182(1): 42-9.
3. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. BMJ **2021**; 375: e068060.
4. Song JY, Yoon JG, Seo YB, et al. Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial. J Clin Med **2021**; 10(16): 3545.
5. Accelerating Covid-19 Therapeutic I, Vaccines -6 Study G, Naggie S. Inhaled Fluticasone for Outpatient Treatment of Covid-19: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial. medRxiv **2022**.
6. Agusti A, De Stefano G, Levi A, et al. Add-on inhaled budesonide in the treatment of hospitalised patients with COVID-19: a randomised clinical trial. Eur Respir J **2022**; 59(3).
7. Duvignaud A, Lhomme E, Onaisi R, et al. Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE). Clin Microbiol Infect **2022**; 28(7): 1010-6.
8. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med **2021**; 9(7): 763-72.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tocilizumab	no tocilizumab	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 28 days to 30 days)												
8 [1-8]	randomized trials	not serious [a]	not serious	not serious	serious [b]	none	810/3280 (24.7%)	893/3054 (29.2%)	**RR 0.91** (0.79 to 1.04)	**26 fewer per 1,000** (from 61 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical deterioration (follow-up: range 14 days to 30 days)												
7 [1-6,8]	randomized trials	serious [c]	not serious	not serious [d]	not serious	none	799/2712 (29.5%)	939/2503 (37.5%)	**RR 0.83** (0.77 to 0.89)	**64 fewer per 1,000** (from 86 fewer to 41 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events												
7 [1-7,e]	randomized trials	serious [c]	not serious	not serious	serious [f]	none	210/1249 (16.8%)	141/946 (14.9%)	**RR 0.89** (0.74 to 1.07)	**16 fewer per 1,000** (from 39 fewer to 10 more)	⨁⨁◯◯ LOW	CRITICAL

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

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

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

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

Explanations

a. 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 PaO_2/FiO_2 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

1. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med **2021**; 384(16): 1491-502.
2. Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.08.27.20183442 [Preprint 12 September 2020].
3. Hermine O, Mariette X, Tharaux PL, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med **2020**; 181(1): 32-40.
4. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med **2021**; 384(1): 20-30.
5. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med **2020**; 181(1): 24-31.
6. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med **2020**; 383: 2333-44.
7. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ **2021**; 372: n84.
8. Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. Lancet **2021**; 397(10285): 1637-45.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sarilumab	no sarilumab	Relative (95% CI)	Absolute (95% CI)		
Mortality (assessed with: indirect estimate from network meta-analysis)												
18 [1,a]	randomized trials	not serious	not serious	not serious	very serious [b]	none	Network estimate: **OR: 0.80**; 95%: CI: 0.61, 1.04 Direct estimate: **OR: 0.98**; 95% CI: 0.62, 1.56 Indirect estimate: **OR: 0.72**; 95% CI: 0.52, 0.99				⨁⨁◯◯ LOW	CRITICAL
Clinical deterioration (follow-up: 21 days; assessed with: progression to intubation, ECMO, or death)												
2 [2,3]	randomized trials	serious [c]	not serious [d]	not serious [e]	very serious [f]	none	72/305 (23.6%)	157/341 (46.0%) [g]	**RR 0.67** (0.42 to 1.05)	**152 fewer per 1,000** (from 267 fewer to 23 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (follow-up: 21 days)												
4 [2-4]	randomized trials	serious [c]	not serious	not serious	serious [h]	none	566/1520 (37.2%)	158/795 (19.9%)	**RR 1.03** (0.89 to 1.18)	**6 more per 1,000** (from 22 fewer to 36 more)	⨁⨁◯◯ LOW	CRITICAL

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

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

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

CI: Confidence interval; **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 (I^2=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

1. Godolphin PJ, Fisher DJ, Berry LR, et al. Association between tocilizumab, sarilumab and all-cause mortality at 28 days in hospitalized patients with COVID-19: A network meta-analysis. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.08.26.21262523 [Preprint 28 August 2021].
2. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med **2021**; 384(16): 1491-502.
3. Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med **2021**; 9(5): 522-32.
4. Sivapalasingam S, Lederer D, Bhore R, et al. A Randomized Placebo-Controlled Trial of Sarilumab in Hospitalized Patients with Covid-19. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.05.13.21256973 [Preprint 14 May 2021].

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)		
Mortality (RCTs) (follow-up: range 15 days to 60 days)												
18 [1-18]	randomized trials	not serious [a,b]	not serious	not serious	serious [c]	none	2163/9082 (23.8%)	2007/8150 (24.6%)	**RR 0.98** (0.93 to 1.03)	**5 fewer per 1,000** (from 17 fewer to 7 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation												
4 [3,6,9,14]	randomized trials	serious [d]	not serious	not serious	serious [e]	none	184/581 (31.7%)	166/471 (35.2%)	**RR 1.10** (0.94 to 1.29)	**35 more per 1,000** (from 21 fewer to 102 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (transfusion-associated circulatory overload, transfusion-related acute lung injury, severe allergic transfusion reaction) (follow-up: 4 hours)												
1 [19]	observational studies	extremely serious [f]	not serious	not serious	not serious	none	SAEs from 20,000 transfused patients: Within first 4 hours, of the SAEs, 63 deaths were reported (0.3% of all transfusions) and 13 of those deaths were judged as possibly or probably related to the transfusion of COVID-19 convalescent plasma. There were 83 non-death SAEs reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion-related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction.				⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (mortality, cardiac, thrombotic, sustained hypotensive events requiring intervention) (follow-up: 7 days)												
1 [19]	observational studies	extremely serious [f]	not serious	not serious	not serious	none	SAEs from 20,000 transfused patients: Within 7 days of transfusion, 1711 deaths (8.56%) and 1136 serious adverse events (5.68%) were reported. Non-mortality SAEs included: 643 cardiac events (569 judged as unrelated to the transfusion); 406 sustained hypotensive events requiring intravenous pressor support; and 87 thromboembolic or thrombotic events (55 judged as unrelated to the transfusion).				⨁◯◯◯ VERY LOW	CRITICAL
Any adverse events (RCTs)												
11 [3,4,6,8,11-13,15-18]	randomized trials	serious [d]	not serious	not serious [g]	serious [h]	none	574/2843 (20.2%)	307/1959 (15.7%)	**RR 1.08** (0.94 to 1.26)	**13 more per 1,000** (from 9 fewer to 41 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

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

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.

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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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: range 15 days to 28 days) [a]												
3 [1-3]	randomized trials	not serious	not serious	not serious	very serious [b]	none	3/929 (0.3%)	7/923 (0.8%)	**RR 0.53** (0.14 to 1.98)	**4 fewer per 1,000** (from 7 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL
COVID-19 related hospitalizations, ED/urgent care visits, or death (follow-up: 15 days)												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [c]	none	94/849 (11.1%)	118/843 (14.0%)	**RR 0.79** (0.62 to 1.00)	**29 fewer per 1,000** (from 53 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalizations (all-cause) (follow-up: range 15 days to 28 days)												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [d]	none	73/867 (8.4%)	98/869 (11.3%)	**RR 0.74** (0.56 to 0.98)	**29 fewer per 1,000** (from 50 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Progression to severe respiratory disease (follow-up: 15 days; assessed with: defined as a respiratory rate of ≥30 breaths per minute, SaO_2 < 93% on room air, or both)												
1 [2]	randomized trials	not serious [e]	not serious	serious [f]	serious [g]	none	13/80 (16.3%)	25/80 (31.3%)	**RR 0.52** (0.29 to 0.94)	**150 fewer per 1,000** (from 222 fewer to 19 fewer)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events: serious transfusion reactions (requiring treatment or admission) (follow-up: 15 days)												
2 [1,3]	randomized trials	not serious	not serious	not serious	very serious [c]	none	5/849 (0.6%)	0/843 (0.0%)	**RR 5.95** (0.72 to 49.29) [h]	**6 more per 1,000** (from 1 more to 11 more) [i]	⨁⨁◯◯ LOW	CRITICAL
Any adverse events (follow-up: 15 days)												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [c]	none	127/849 (15.0%)	147/843 (17.4%)	**RR 0.86** (0.70 to 1.05)	**24 fewer per 1,000** (from 52 fewer to 9 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

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

CI: Confidence interval; **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

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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

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

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

Publication bias: Selective publication of studies

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

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

Explanations

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

Reference

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

Table 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

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

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

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

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

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

Explanations

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

Reference

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

Table 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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remdesivir	no remdesivir	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 28 days to 29 days)												
3 [1-3]	randomized trials	serious [a,b,c]	not serious	not serious	serious [d]	none	369/2726 (13.5%)	374/2593 (14.4%)	**RR 0.92** (0.77 to 1.10)	**12 fewer per 1,000** (from 33 fewer to 14 more)	⨁⨁◯◯ LOW	CRITICAL
Time to recovery (follow-up: 29 days)												
1 [2]	randomized trials	serious [c]	not serious	not serious	not serious	none	345/486 (71.0%)	306/471 (65.0%)	**Rate ratio 1.31** (1.12 to 1.52)	**97 more per 1,000** (from 41 more to 147 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical improvement (follow-up: 28 days)												
1 [1]	randomized trials	not serious [a,b]	not serious	not serious	very serious [d]	none	103/158 (65.2%)	45/78 (57.7%)	**RR 1.13** (0.91 to 1.41)	**75 more per 1,000** (from 52 fewer to 237 more)	⨁⨁◯◯ LOW	CRITICAL
Need for mechanical ventilation (follow-up: 29 days)												
1 [2]	randomized trials	not serious	not serious	not serious	serious [e]	none	52/402 (12.9%)	82/364 (22.5%)	**RR 0.57** (0.42 to 0.79)	**97 fewer per 1,000** (from 131 fewer to 47 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (grade 3/4)												
2 [1,2]	randomized trials	not serious	not serious	not serious	serious [f]	none	44/632 (7.0%)	53/545 (8.9%)	**RR 0.79** (0.54 to 1.16)	**20 fewer per 1,000** (from 45 fewer to 16 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalization												
1 [1]	randomized trials	not serious [a,b]	not serious	not serious	very serious [d]	none	158	78	-	MD **1 days higher** (0.12 higher to 1.88 higher)	⨁⨁◯◯ LOW	IMPORTANT

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

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

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

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

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

Explanations

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

References

1. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet **2020**; 395(10236): 1569-78.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med **2020**; 383(19): 1813-26.
3. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.

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

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

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
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

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med **2020**; 383(19): 1813-26.
2. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.
3. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet **2020**; 395(10236): 1569-78.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high-dose famotidine (80 mg tid)	no famotidine	Relative (95% CI)	Absolute (95% CI)		
Symptom resolution (follow-up: 28 days) [a]												
1[1]	randomized trials	not serious	not serious	not serious	very serious [b]	none	19/27 (70.4%) [c]	18/28 (64.3%)	**RR 1.10** (0.76 to 1.58)	**64 more per 1,000** (from 154 fewer to 373 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events [d]												
1[1]	randomized trials	not serious	not serious	not serious	very serious [b]	none	2/27 (7.4%)	3/28 (10.7%)	**RR 0.69** (0.13 to 3.80)	**33 fewer per 1,000** (from 93 fewer to 300 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

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

1. Brennan CM, Nadella S, Zhao X, et al. Oral famotidine versus placebo in non-hospitalised patients with COVID-19: a randomised, double-blind, data-intense, phase 2 clinical trial. Gut **2022**; 71(5): 879-88.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	famotidine	no famotidine	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	8/89 (9.0%)	9/89 (10.1%)	**RR 0.89** (0.36 to 2.20)	**11 fewer per 1,000** (from 65 fewer to 121 more)	⨁⨁◯◯ LOW	CRITICAL
Mechanical ventilation												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	21/89 (23.6%)	24/89 (27.0%)	**RR 0.88** (0.53 to 1.45)	**32 fewer per 1,000** (from 127 fewer to 121 more)	⨁⨁◯◯ LOW	CRITICAL
ICU care												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	18/89 (20.2%)	20/89 (22.5%)	**RR 0.90** (0.51 to 1.58)	**22 fewer per 1,000** (from 110 fewer to 130 more)	⨁⨁◯◯ LOW	CRITICAL
Time to symptom-free												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	89	89	-	MD **0.9 days fewer** (1.44 fewer to 0.36 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Length of hospital stay												
1[1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	89	89	-	MD **1.7 days fewer** (2.77 fewer to 1.13 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	famotidine	no famotidine	Relative (95% CI)	Absolute (95% CI)		
0	observational studies						Post-marketing and registrational reported common adverse events include constipation (1.2%-1.4%), diarrhea (1.7%), dizziness (1.3%) and headache (1%-4.7%), but overall famotidine is well tolerated. Rare but serious adverse events (<1%) include: Stevens-Johnson syndrome, toxic epidermal necrolysis, necrotizing enterocolitis, anaphylaxis, angioedema, rhabdomyolysis, seizure, hospital-acquired pneumonia, interstitial pneumonia. (Micromedex)				-	CRITICAL

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

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

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

CI: Confidence interval; **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

1. Pahwani S, Kumar M, Aperna F, et al. Efficacy of Oral Famotidine in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2. Cureus **2022**; 14(2): e22404

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib	no baricitinib	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 28 days to 60 days)												
2[1,2]	randomized trials	not serious	not serious	not serious	serious [a]	none	592/4912 (12.1%)	662/4769 (13.9%)	**RR 0.87** (0.78 to 0.96)	**18 fewer per 1,000** (from 31 fewer to 6 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Mechanical ventilation (follow-up: 28 days)												
1[2]	randomized trials	not serious	not serious	not serious	serious [a]	none	283/4014 (7.1%)	322/3891 (8.3%)	**RR 0.85** (0.73 to 0.99)	**12 fewer per 1,000** (from 22 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Disease progression (follow-up: 28 days; assessed with: progression to high-flow oxygen, non-invasive ventilation oxygen, invasive mechanical ventilation, or death)												
1[3]	randomized trials	not serious	not serious	not serious	serious [a]	none	212/764 (27.7%)	232/761 (30.5%)	**OR 0.85** (0.67 to 1.08)[b]	**33 fewer per 1,000** (from 78 fewer to 17 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events (follow-up: 28 days)												
1[3]	randomized trials	not serious	not serious	not serious	serious [c,d]	none	110/750 (14.7%) [e]	135/752 (18.0%)	**RR 0.82** (0.65 to 1.03)	**32 fewer per 1,000** (from 63 fewer to 5 more)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Risk of bias: Study limitations **Inconsistency:** Unexplained heterogeneity across study findings **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

1. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med **2021**; 9(12): 1407-18.
2. RECOVERY Collaborative Group, Horby PW, Emberson JR, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.03.02.22271623 [Preprint 3 March 2022].
3. Marconi VC, Ramanan AV, de Bono S, et al. Baricitinib plus Standard of Care for Hospitalized Adults with COVID-19. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.04.30.21255934 [Preprint 3 May 2021].

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib	no baricitinib	Relative (95% CI)	Absolute (95% CI)		
Mortality (HR) (follow-up: 60 days)												
2[1,2]	randomized trials	not serious	not serious	not serious	serious [a]	none	61/185 (33.0%)	75/167 (44.9%)	**RR 0.74** (0.57 to 0.97)	**117 fewer per 1,000** (from 193 fewer to 13 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Invasive mechanical ventilation free days (follow-up: 60 days)												
1[1]	randomized trials	not serious	not serious	not serious	very serious [a,b]	none	51	50	-	MD **2.36 vent free days more** (6.1 more to 1.4 fewer) [c]	⨁⨁◯◯ LOW	IMPORTANT
Days of hospitalization (follow-up: 60 days)												
1[1]	randomized trials	not serious	not serious	not serious	very serious [a,d]	none	51	50	-	MD **2.3 days fewer** (4.6 fewer to 0)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow-up: 28 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	25/50 (50.0%)	35/49 (71.4%)	**RR 0.70** (0.50 to 0.97)	**214 fewer per 1,000** (from 357 fewer to 21 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

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

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

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

CI: Confidence interval; **HR:** Hazard Ratio; **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

1. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. Lancet Respir Med **2022**; 10(4): 327-36.
2. RECOVERY Collaborative Group, Horby PW, Emberson JR, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.03.02.22271623 [Preprint 3 March 2022].

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib + RDV	RDV	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	24/515 (4.7%)	37/518 (7.1%)	**HR 0.65** (0.39 to 1.09)	**24 fewer per 1,000** (from 43 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical recovery - hospitalized requiring supplemental O_2/receiving noninvasive ventilation or high-flow O_2 (ordinal 5+6) (assessed with: Ordinal scale <4)												
1 [1]	randomized trials	serious [b]	not serious	not serious	serious [c]	none	344/391 (88.0%)	316/389 (81.2%)	**RR 1.08** (1.02 to 1.15)	**65 more per 1,000** (from 16 more to 122 more)	⨁⨁◯◯ LOW	CRITICAL
Clinical recovery - receiving noninvasive ventilation or high-flow O_2, invasive mechanical ventilation or ECMO (ordinal 6+7; stratified) (assessed with: Ordinal scale <4)												
1 [1]	randomized trials	not serious [d]	not serious	not serious	serious [e]	none	122/176 (69.3%)	114/191 (59.7%)	**HR 1.29** (1.00 to 1.66) [d]	**93 more per 1,000** (from 0 fewer to 182 more)	⨁⨁⨁◯ MODERATE	CRITICAL
New use of mechanical ventilation or ECMO (follow-up: 29 days)												
1 [1]	randomized trials	serious [f]	not serious	not serious	serious [g]	none	46/461 (10.0%)	70/461 (15.2%)	**RR 0.66** (0.46 to 0.93)	**52 fewer per 1,000** (from 82 fewer to 11 fewer)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [g]	none	81/507 (16.0%)	107/509 (21.0%)	**RR 0.76** (0.59 to 0.99) [h]	**50 fewer per 1,000** (from 86 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

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

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **OR:** Odds ratio; **RDV**: Remdesivir

Explanations

a. 95% CI includes substantial benefits as well as substantial harms
b. Non-stratified subgroup post hoc analysis.
c. Lower boundary of the 95% CI crosses our threshold for a meaningful difference.
d. Data from table S6. Although described as "analysis as randomized" in this stratum of severe COVID-19 patients, the analysis included moving patient from a baseline of "moderate" to "severe" 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.
e. 95% CI includes substantial benefits as well as no effect
f. Not a predefined stratum. Secondary analysis.
g. Less than 300 events; concern for fragility
h. 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.

Reference

1. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med **2021**; 384: 795-807.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tofacitinib	no tofacitinib	Relative (95% CI)	Absolute (95% CI)		
Death or respiratory failure (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [a,b]	none	26/144 (18.1%)	42/145 (29.0%)	**RR 0.63** (0.41 to 0.97)	**107 fewer per 1,000** (from 171 fewer to 9 fewer)	⨁⨁◯◯ LOW	CRITICAL
Mortality (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [a,c]	none	4/144 (2.8%)	8/145 (5.5%)	**RR 0.49** (0.15 to 1.63)	**28 fewer per 1,000** (from 47 fewer to 35 more)	⨁⨁◯◯ LOW	CRITICAL
Progression to mechanical ventilation or ECMO (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [a]	none	1/144 (0.7%)	4/145 (2.8%)	**RR 0.25** (0.03 to 2.20)	**21 fewer per 1,000** (from 27 fewer to 33 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [a,c]	none	20/142 (14.1%) [d]	17/142 (12.0%)	**RR 1.18** (0.64 to 2.15)	**22 more per 1,000** (from 43 fewer to 138 more)	⨁⨁◯◯ LOW	CRITICAL

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

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

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

1. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med **2021**; 385(5): 406-15.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	no ivermectin	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 14 days to 28 days)												
11 [1-11]	randomized trials	not serious [a]	not serious [b]	not serious	serious [c]	none	66/1033 (6.4%)	53/937 (5.7%)	**RR 0.85** (0.40 to 1.84)	**8 fewer per 1,000** (from 34 fewer to 48 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation (follow-up: 28 days)												
3 [7,8,11]	randomized trials	serious [d]	not serious	not serious	very serious [c]	none	13/594 (2.2%)	28/583 (4.8%)	**RR 0.45** (0.24 to 0.86)	**26 fewer per 1,000** (from 37 fewer to 7 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Symptom resolution (follow-up: 7 days)												
1 [12]	randomized trials	serious [d]	not serious	not serious	very serious [c]	none	16/25 (64.0%)	15/25 (60.0%)	**RR 1.07** (0.69 to 1.65)	**42 more per 1,000** (from 186 fewer to 390 more)	⨁◯◯◯ VERY LOW	CRITICAL
Viral clearance at day 7 (RCT) (follow-up: range 7 days to 29 days)												
6 [4,5,8,10,13,14]	randomized trials	serious [e]	serious [f]	serious [g]	very serious [c]	none	77/202 (38.1%)	55/158 (34.8%)	**RR 1.06** (0.74 to 1.52)	**21 more per 1,000** (from 91 fewer to 181 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (follow-up: 28 days)												
6 [2,4,7,8,9,11]	randomized trials	not serious	not serious	not serious	serious [c]	none	38/734 (5.2%)	52/712 (7.3%)	**RR 1.03** (0.32 to 3.34)	**2 more per 1,000** (from 50 fewer to 171 more)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
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.

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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

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

7 [2,3,5,8,10,11,16]	randomized trials	not serious	not serious	not serious	serious [j]	none	31/1973 (1.6%)	40/1933 (2.1%)	**RR 0.81** (0.51 to 1.30)	**4 fewer per 1,000** (from 10 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
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 I2=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.

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1. Hashim HA, Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.10.26.20219345 [Preprint 27 October 2020].
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Fluvoxamine

Evidence profiles

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

Table 26. GRADE evidence profile, Recommendation 25
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							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	fluvoxamine	no fluvoxamine	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days) [a]												
2 [1,2]	randomized trials	not serious	not serious	not serious	very serious [b]	none	17/821 (2.1%)	25/828 (3.0%)	**RR 0.69** (0.38 to 1.27)	**9 fewer per 1,000** (from 19 fewer to 8 more)	⨁⨁◯◯ LOW	CRITICAL
Hospitalization, emergency room visits (>6 hours), or oxygen saturation <92% (follow up: 28 days) [a]												
2 [1,2]	randomized trials	not serious	not serious	serious [c]	serious [b]	none	79/821 (9.6%)	125/828 (15.1%)	**RR 0.64** (0.50 to 0.84)	**54 fewer per 1,000** (from 75 fewer to 24 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hospitalization for COVID-19 (follow up: 28 days) [a]												
2 [1,2]	randomized trials	not serious	not serious	not serious	very serious [b]	none	76/821 (9.3%)	103/828 (12.4%)	**RR 0.75** (0.57 to 0.99)	**31 fewer per 1,000** (from 53 fewer to 1 fewer)	⨁⨁◯◯ LOW	CRITICAL
Viral clearance (follow up: 7 days)												
1 [2]	randomized trials	serious [d]	not serious	serious [e]	very serious [b]	none	40/207 (19.3%)	58/221 (26.2%)	**RR 0.74** (0.52 to 1.05)	**68 fewer per 1,000** (from 126 fewer to 13 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events [a]												
2 [1,2]	randomized trials	not serious	not serious	not serious	very serious [f]	none	60/821 (7.3%)	75/828 (9.1%)	**RR 0.81** (0.59 to 1.12)	**17 fewer per 1,000** (from 37 fewer to 11 more)	⨁⨁◯◯ LOW	CRITICAL

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

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

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

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

1. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA **2020**; 324(22): 2292-300.
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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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nirmatrelvir/ ritonavir	no nirmatrelvir/ ritonavir	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 28 days)												
1[1]	randomized trials	serious [a]	not serious	not serious [b]	serious [c]	none	0/1039 (0.0%)	12/1046 (1.1%)	**RR 0.04** (0.00 to 0.68)	**11 fewer per 1,000** (from 18 fewer to 5 fewer) [d]	⨁⨁◯◯ LOW	CRITICAL
COVID-19-related hospitalizations (follow-up: 28 days)												
1[1]	randomized trials	serious [a]	not serious	not serious [b,e]	serious [c]	none	8/1039 (0.8%)	65/1046 (6.2%)	**RR 0.12** (0.06 to 0.26)	**55 fewer per 1,000** (from 58 fewer to 46 fewer)	⨁⨁◯◯ LOW	CRITICAL
COVID-19-related hospitalization or all-cause death (follow-up: 28 days)												
1[1]	randomized trials	serious [a]	not serious	not serious [b]	serious [c]	none	8/1039 (0.8%)	66/1046 (6.3%)	**RR 0.12** (0.06 to 0.25)	**56 fewer per 1,000** (from 59 fewer to 47 fewer)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events - not reported												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

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

NB: Certainty ratings 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

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid™. Available at: https://www.fda.gov/media/155050/download. Accessed 3 February 2022.

Figure 2. FDA EUA criteria for the use of nirmatrelvir/ritonavir co-packaged as Paxlovid™ [1]

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

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.

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 [1]*

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide
- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- 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

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 3 November 2022.

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 [1]

- 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

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 3 November 2022.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	molnupiravir	no molnupiravir	Relative (95% CI)	Absolute (95% CI)		
COVID-19-related mortality (follow-up: range 28 days to 29 days)												
2 [1,2]	randomized trials	not serious	not serious	not serious [a]	very serious [b,c]	none	1/764 (0.1%)	9/761 (1.2%)	**RR 0.11** (0.01 to 0.86)	**11 fewer per 1,000** (from 12 fewer to 2 fewer)	⨁⨁◯◯ LOW	CRITICAL
COVID-19-related hospitalizations (follow-up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious [d,e]	very serious [c,f]	none	45/709 (6.3%)	64/699 (9.2%)	**RR 0.68** (0.48 to 1.00)	**29 fewer per 1,000** (from 48 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hospitalization or death (all-cause) (follow-up: 29 days)												
1 [1]	randomized trials	not serious	not serious	not serious [e]	very serious [b,c]	none	48/709 (6.8%)	68/699 (9.7%)	**HR 0.69** (0.48 to 1.01)	**29 fewer per 1,000** (from 49 fewer to 1 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow-up: range 28 days to 29 days)												
2 [1,2]	randomized trials	not serious	not serious	not serious	very serious [f,g]	none	6/765 (0.8%)	14/763 (1.8%)	**RR 0.43** (0.17 to 1.11)	**10 fewer per 1,000** (from 15 fewer to 2 more)	⨁⨁◯◯ LOW	CRITICAL

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

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

NB: Certainty ratings 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

1. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med **2021**: Available at: https://doi.org/10.1056/nejmoa2116044 [Epub ahead of print 16 December 2021].
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Figure 5. FDA EUA criteria for the use of molnupiravir [1]

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

1. U.S. Food and Drug Administration. Fact Sheet for Patients And Caregivers: Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019 (COVID-19). Available at: https://www.fda.gov/media/155055/download. Accessed 3 November 2022.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	colchicine	no colchicine	Relative (95% CI)	Absolute (95% CI)		
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 [1-3,9]	randomized trials	serious [c]	serious [d]	not serious	serious [a,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

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

1. Mareev VY, Orlova YA, Plisyk AG, et al. Proactive anti-inflammatory therapy with colchicine in the treatment of advanced stages of new coronavirus infection. The first results of the COLORIT study. Kardiologiia **2021**; 61(2): 15-27.
2. Alsultan M, Obeid A, Alsamarrai O, et al. Efficacy of Colchicine and Budesonide in Improvement Outcomes of Patients with Coronavirus Infection 2019 in Damascus, Syria: A Randomized Control Trial. Interdiscip Perspect Infect Dis **2021**; 2021: 2129006.
3. Lopes MI, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. RMD Open **2021**; 7(1): e001455.
4. Diaz R, Orlandini A, Castellana N, et al. Effect of Colchicine vs Usual Care Alone on Intubation and 28-Day Mortality in Patients Hospitalized With COVID-19: A Randomized Clinical Trial. JAMA Netw Open **2021**; 4(12): e2141328.
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10. Gorial FI, Maulood MF, Abdulamir AS, Alnuaimi AS, Abdulrrazaq MK, Bonyan FA. Randomized controlled trial of colchicine add on to the standard therapy in moderate and severe corona virus Disease-19 infection. Ann Med Surg (Lond) **2022**; 77: 103593.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	colchicine	no colchicine	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3 [1-3]	randomized trials	not serious [a]	not serious	not serious	serious [b]	none	5/2431 (0.2%)	11/2426 (0.5%)	**RR 0.50** (0.19 to 1.33)	**2 fewer per 1,000** (from 4 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalization												
2 [1,3]	randomized trials	not serious [a]	not serious	not serious [c]	serious [d]	none	107/2391 (4.5%)	131/2386 (5.5%)	**RR 0.82** (0.64 to 1.05)	**10 fewer per 1,000** (from 20 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [b]	none	10/2230 (0.4%)	20/2204 (0.9%)	**RR 0.50** (0.24 to 1.07)	**5 fewer per 1,000** (from 7 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events												
1 [1]	randomized trials	not serious	not serious	not serious	serious [b,e]	none	108/2195 (4.9%)	139/2217 (6.3%)	**RR 0.78** (0.61 to 1.00)	**14 fewer per 1,000** (from 24 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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

NB: Certainty ratings may be derived from evidence that 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

1. Tardif J-C, Bouabdallaoui N, L'Allier PL, et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.01.26.21250494 [Preprint 27 January 2021].
2. Gorial FI, Maulood MF, Abdulamir AS, Alnuaimi AS, Abdulrrazaq MK, Bonyan FA. Randomized controlled trial of colchicine add on to the standard therapy in moderate and severe corona virus Disease-19 infection. Ann Med Surg (Lond) **2022**; 77: 103593.
3. Dorward J, Yu L-M, Hayward G, et al. Colchicine for COVID-19 in adults in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.09.20.21263828 [Preprint 23 September 2021].

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

Severity of COVID-19
Mild-to-moderate COVID-19 (SpO_2 ≥94% on room air and not needing supplemental oxygen) with risk factors for progression to severe disease, hospitalization or death [a]
Severe but not critical COVID-19 (SpO_2<94% on room air or needing low-flow supplemental oxygen)
Critical COVID-19 needing high-flow oxygen/ or non-invasive ventilation
Critical COVID-19 needing mechanical ventilation or ECMO

ECMO: Extracorporeal membrane oxygenation; **SpO_2:** 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

Characteristic or concern	Therapeutic agents
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 [a] (specific cut-offs to be mentioned for each agent)	• Tofacitinib- warning to avoid when lymphocytes <500 cells/mm3, neutrophils <1000 cells/mm^3, or hemoglobin <9 g/dL • Baricitinib- warning to avoid when lymphocytes <500 cells/mm3, neutrophils <1000 cells/mm^3, or hemoglobin <8 g/dL • Tocilizumab- associated with neutropenia and thrombocytopenia; warning to avoid for chronic use when ANC <2000 cells/mm^3 or platelets <100,000 per mm3 • Sarilumab- associated with neutropenia and thrombocytopenia; warning to avoid for chronic use when ANC <2000 cells/mm^3 or platelets <150,000 per mm^3
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.

Characteristic or concern	Therapeutic agents
Age (pediatric and adolescent) [b]	• Molnupiravir is suggested for patients ≥18 years • Tocilizumab is suggested for patients ≥2 years • Sarilumab is suggested for patients ≥18 years • Baricitinib is suggested for patients ≥2 years • Tofacitinib is suggested for patients ≥2 years • Neutralizing antibodies are suggested for patients ≥12 years • Nirmatrelvir/ritonavir is suggested for patients ≥12 years • Remdesivir is indicated for all ages • Dexamethasone is indicated for all ages
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

Care location and COVID-19 severity	Pharmacologic treatments available in the United States
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)* Can be considered in patients with mild-moderate COVID-19 hospitalized for other reasons	• 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.
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

Care location and COVID-19 severity	Pharmacologic treatments available in the United States
	• 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 makers • 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])

	MIS-C (CDC 2020)[1]	**PIMS-TS or PMIS (Royal College of Paediatrics and Child Health 2020)[2]**
Includes	Age <21 years presenting with: • Fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours) • 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), • Evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)	A child presenting with: • Persistent fever >38.5°C • Laboratory evidence of inflammation (neutrophilia, elevated CRP and lymphopenia) • Evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (listed in Appendix of reference)
Excludes	Patients with alternative plausible diagnoses	Patients with any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus
Other criteria	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	SARS-CoV-2 PCR testing may be positive or negative

References

1. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed 23 November 2021.
2. Royal College of Paediatrics and Child Health. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19, **2020**.