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	Hydroxychloroquine	no HCQ	Relative (95% CI)	Absolute (95% CI)		
Mortality (RCTs) (follow up: range 22 days to 49 days)												
5 [1,2,3,4,5]	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												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxychloroquine	no HCQ	Relative (95% CI)	Absolute (95% CI)		
4 [2,7,8,9]	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
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

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 adverse events include diarrhea, fatigue and transient AST elevation. Chen Z 2020: 1 rash, 1 headache. Tang 2020: 21 adverse events include disease progression (1%), URI (1%), diarrhea (10%), vomiting (3%).
k. 3 adverse events reported in 2 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 adverse events 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].