

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 HCQ	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 ^{2,3,4}	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)(Ip, Magagnoli 2020, Rosenberg 2020).			⊕○○○ 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 ^{5,6,7}	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 HCQ	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
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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
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GRADE Working Group grades of evidence

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

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

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

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

Risk of bias: Study limitations

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

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

Publication bias: Selective publication of studies

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.

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- 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

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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].