### Table 2. GRADE evidence profile, PICO 2

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

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Nr of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydroxychloroquine and azithromycin</td>
<td>no HCQ/azithromycin</td>
</tr>
<tr>
<td></td>
<td>Relatively (95% CI)</td>
<td>Absolutely (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 ¹ ² ³</td>
<td>observational studies</td>
</tr>
<tr>
<td><strong>Virologic Failure</strong></td>
<td>2 ⁴ ⁵ ⁶</td>
<td>observational studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Significant QT prolongation</strong></td>
<td>2 ⁶ ⁷</td>
<td>observational studies</td>
</tr>
</tbody>
</table>

### Adverse events
<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>observational studies</td>
<td>serious k</td>
<td>not serious</td>
<td>not serious</td>
<td>serious k</td>
</tr>
</tbody>
</table>

Several case reports of QT prolongation related to hydroxychloroquine have been published. In another prospective cohort study in 224 patients with SLE who received either chloroquine or hydroxychloroquine, gastrointestinal side effects occurred in 7% of patients.8 Several case reports have been published citing the risk of a prolonged QT prolongation, torsades de pointes, and ventricular tachycardia in patients receiving azithromycin. In a large cohort study, patients taking a 5 day course of azithromycin had an increased risk of sudden cardiac death with a hazard ratio of 2.71 (1.58-4.64) vs. 0.85 (0.45-1.60), compared to no antibiotic or amoxicillin, respectively.9 Given that both medications have QT prolonging effects, any combination is likely to substantially increase the risk of clinically relevant harmful effects.8,9

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. Concerns with unmeasured and residual confounding. Multiple co-interventions received across arms.
b. The 95% CI includes the potential for both benefit and harm.
c. No contemporaneous control groups; no adjustment for baseline severity, resulting in high risk for residual confounding
d. 2 case series from France showed divergent results
e. Surrogate marker for mortality or resolution of COVID-19.
f. A very small number of events. Optimal information size not met.
g. 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%).

h. Gautret reported on a historical viral clearance rate in symptomatic patients from a separate hospital. Criteria for selection of patient remains unclear, as presumably a sizable number of untreated patients could have been available with data on viral clearance.

i. 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.

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

k. Case reports

References


