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SPECIAL ARTICLE

# Should Clinicians Use Chloroquine or Hydroxychloroquine Alone or in Combination With Azithromycin for the Prophylaxis or Treatment of COVID-19? Living Practice Points From the American College of Physicians (Version 1)

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## Key Question 1

Should Clinicians Use Chloroquine or Hydroxychloroquine Alone or in Combination With Azithromycin for Prophylaxis Against COVID-19?

## Key Question 2

Should Clinicians Use Chloroquine or Hydroxychloroquine Alone or in Combination With Azithromycin for Treatment of COVID-19?

## Background

Using chloroquine or hydroxychloroquine, with or without azithromycin, to prevent coronavirus disease (COVID-19) after infection with novel coronavirus (SARS-CoV-2) or to treat COVID-19 began to receive attention following preliminary reports from in vitro (1) and human (2) studies. While multiple studies are planned or under way (3, 4), it is imperative to continually synthesize the results from the best available evidence to inform point-of-care decisions about the use of chloroquine or hydroxychloroquine. These practice points are based on a rapid and living systematic evidence review conducted by the University of Connecticut Health Outcomes, Policy, and Evidence Synthesis Group and will be updated as new evidence becomes available. The practice points development and update methods are included in the **Appendix,** available at Annals.org. This version of the practice points, based on an evidence review conducted on 17 April 2020, was approved by the American College of Physicians Board of Regents on 4 May 2020 and submitted to *Annals of Internal Medicine* on 6 May 2020.

## Practice Points

The efficacy of chloroquine or hydroxychloroquine alone or in combination with azithromycin to prevent COVID-19 after infection with SARS-CoV-2 or to treat patients with COVID-19 is not established and future clinical trials are needed to answer these questions. There are known harms of these medications when used to treat other diseases (5, 6). Current evidence about efficacy and harms for use in the context of COVID-19 is sparse, conflicting, and from low quality studies, increasing the uncertainty and lowering our confidence in the conclusions of these studies when assessing the benefits or understanding the balance when compared with harms. These interim practice points are based on best available evidence. We will maintain these practice points as a living guidance document, updated as new evidence becomes available.

- Do not use chloroquine or hydroxychloroquine alone or in combination with azithromycin as prophylaxis against COVID-19 due to known harms and no available evidence of benefits in the general population.
- Do not use chloroquine or hydroxychloroquine alone or in combination with azithromycin as a treatment of patients with COVID-19 due to known harms and no available evidence of benefits in patients with COVID-19.
- In light of known harms and very uncertain evidence of benefit in patients with COVID-19, using shared and informed decision making with patients (and their families), clinicians may treat hospitalized COVID-19–positive patients with chloroquine or hydroxychloroquine alone or in combination with azithromycin in the context of a clinical trial.

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† Nonphysician public representative.

Should chloroquine or hydroxychloroquine alone or in combination with azithromycin be used as prophylaxis against COVID-19 in the general population?

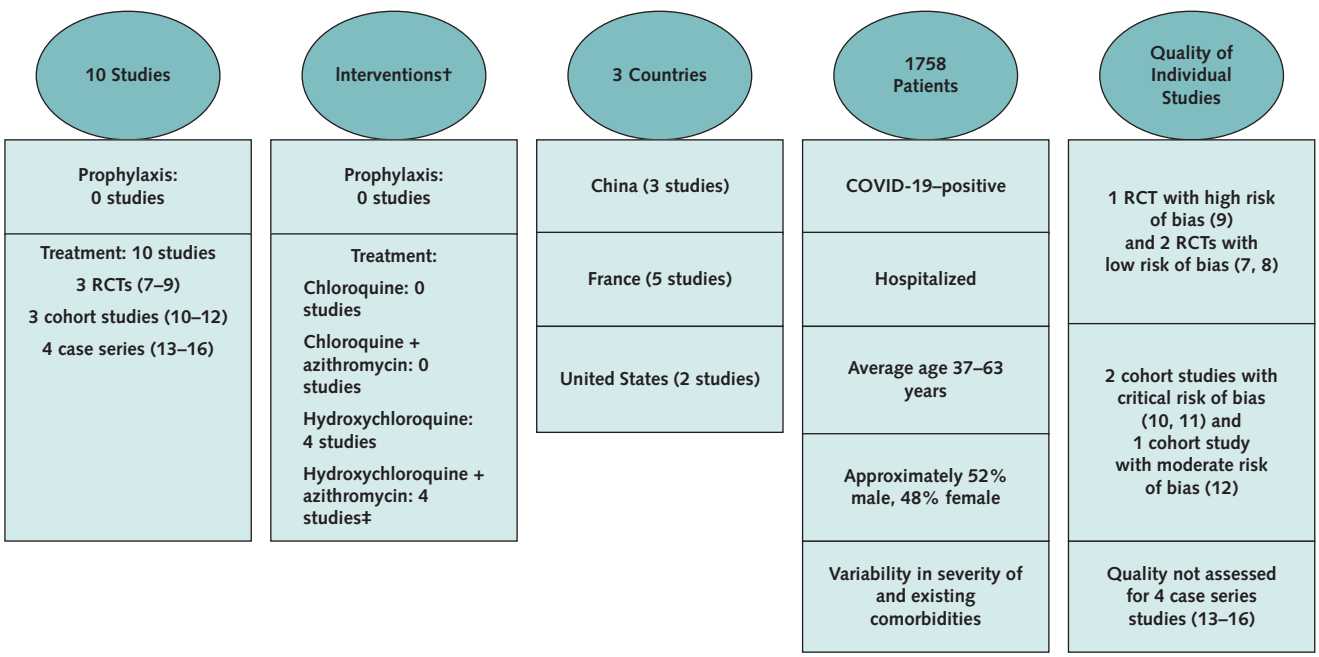
| Interventions | Use? | Rationale |
|---|---|---|
| Chloroquine | NO | No available evidence |
| Chloroquine + Azithromycin | NO | No available evidence |
| Hydroxychloroquine | NO | No available evidence |
| Hydroxychloroquine + Azithromycin | NO | No available evidence |

Should chloroquine or hydroxychloroquine in combination with azithromycin be used for treatment of patients with COVID-19?

| Interventions | Use? | Rationale |
|---|---|---|
| Chloroquine | NO* | No available evidence in COVID-19–positive patients |
| Chloroquine + Azithromycin | NO* | No available evidence in COVID-19–positive patients |
| Hydroxychloroquine | NO* | Insufficient evidence about benefits and harms |
| Hydroxychloroquine + Azithromycin | NO* | Insufficient evidence about benefits and harms |

* In light of known harms and very uncertain evidence of benefit in patients with COVID-19, using shared and informed decision-making with patients (and their families), clinicians may treat hospitalized COVID-19–positive patients with chloroquine or hydroxychloroquine alone or in combination with azithromycin in the context of a clinical trial.

***Figure.*** Evidence Description for COVID-19 Studies*




COVID-19 = coronavirus disease 2019; RCT = randomized controlled trial.
* Evidence search was conducted by the University of Connecticut Health Outcomes, Policy, and Evidence Synthesis Group. Current search for evidence, completed on 17 April 2020, aimed to identify all studies about the use of chloroquine or hydroxychloroquine alone or in combination for prophylaxis or treatment of patients with COVID-19. (See **Supplement**, available at Annals.org.)
† The use and extent of parallel treatment interventions was difficult to determine. For example, in some studies, it was documented that patients received parallel interventions, whereas in other studies there was insufficient information to determine if patients did or did not receive parallel interventions.
‡ In 2 cohort studies (11, 12), the administration of azithromycin was not randomized, precluding judgment of efficacy.

Evidence Summary: What Information Does the Evidence Provide?

**Prophylaxis**

**Evidence for Potential Benefits**

No studies identified

**Evidence for Potential Harms**

No studies identified

**Treatment**

**Evidence for Potential Benefits***

| Outcome | Study Design | Evidence | Certainty of Evidence† |
|---|---|---|---|
| **Hydroxychloroquine alone for treatment of COVID-19** | | | |
| *Conversion of SARS-CoV-2 test result from positive to negative* | 2 RCTs | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on day 7 (86.7% vs. 93.3%) or day 14 (100% vs. 100%) via throat swab, sputum, or lower respiratory tract secretion and the time to negative results was 1 to 9 days for patients treated with hydroxychloroquine alone and 1 to 4 days for those receiving standard treatment in 1 RCT (7) and hydroxychloroquine alone compared standard treatment up to day 23 (85.4% vs. 81.3%) via upper and/or lower tract specimens or the time to negative results (8 days vs. 7 days) in another RCT (9). | Insufficient |
| | 1 OBS | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on the conversion to negative on day 3 (50% vs. 6%), day 4 (60% vs. 25%), day 5 (65% vs. 19%), and day 6 (70% vs. 13%) via nasopharyngeal PCR in 1 cohort study (11). | |
| *Pulmonary radiologic assessment* | 2 RCTs | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on the progression or exacerbation of pulmonary lesions on CT scan (33.3% vs. 46.7%) in 2 RCTs (7, 8) and radiologic improvement of pneumonia (80.6% vs. 54.8%) in 1 RCT (8). | Insufficient |
| *Resolution of fever, respiratory symptoms, and oxygenation* | 1 RCT | The evidence is very uncertain about the effect of hydroxychloroquine alone (50%) compared with standard treatment (43.6%) in 1 RCT (9). | Insufficient |
| *Resolution of fever* | 2 RCTs | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment in 2 RCTs; median, 1 day vs. 1 day in 1 RCT (7), and mean, 2.2 days vs. 3.2 days in another RCT (7). | Insufficient |
| *Resolution of cough* | 2 RCTs | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (mean 2.0 days vs. 3.1 days) in 1 RCT (8). | Insufficient |
| *Progression to severe disease* | 2 RCTs | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment in 2 RCTs; 6.7% vs. 0% (7, 8). | Insufficient |
| *All-cause mortality* | 1 RCT | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (0% vs. 0%) in 1 RCT (7). | Insufficient |
| | 2 OBS | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment in 2 cohort studies; 12.9% vs. 3.13% (10, 12). | |

*Continued on the following page*

**Treatment**

**Evidence for Potential Benefits***

| Outcome | Study Design | Evidence | Certainty of Evidence† |
|---|---|---|---|
| *Respiratory support* | 1 OBS | The evidence is very uncertain about the effect hydroxychloroquine alone compared with standard treatment on the need at 5 days (+ 0.63 ± 0.79 vs. 0.16 ± 0.64 points) in 1 cohort study (10). | Insufficient |
| *Development of acute respiratory distress syndrome* | 1 OBS | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (27.7% vs. 24.1%) in 1 cohort study (12). | Insufficient |
| *Clinical worsening* | 1 OBS | The evidence is very uncertain about the effect hydroxychloroquine alone compared with standard treatment (20.5% vs. 22.1%) in 1 cohort study on transfer to the ICU within 7 days and/or death from any cause (12). | Insufficient |

**Evidence for Potential Harms**

| Outcome | Study Design | Evidence | Certainty of Evidence† |
|---|---|---|---|
| **Hydroxychloroquine alone for treatment of COVID-19** | | | |
| *Severe adverse events* | 2 RCTs | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment in 2 RCTs; 0% vs. 0% (8, 9). | Insufficient |
| *Any adverse event* | 3 RCTs | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on adverse effects in 3 RCTs; 26.7% vs. 20% (7–9). | |
| | 1 OBS | The evidence is very uncertain about the effect of hydroxychloroquine alone in 1 case series study (11); 8.7% of patients treated with hydroxychloroquine alone experienced adverse events. | Insufficient |
| *Prolonged QTc interval* | 3 OBS | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (8.4% vs. 0%) in 1 cohort study (12). In case series studies, 9% (15) and 11% (13) of patients receiving hydroxychloroquine alone showed a prolonged QTc. | Insufficient |
| *Diarrhea* | 2 RCTs | The evidence is very uncertain about the effect of hydroxychloroquine alone compared with standard treatment; 13.3% vs. 0% (7) and 10% vs. 0% (9). | Insufficient |
| | 1 OBS | The evidence is very uncertain about the effect of hydroxychloroquine alone in 1 cohort study (11); 8.7% patients treated with hydroxychloroquine alone experienced diarrhea. | |
| *Abnormal liver function* | 1 RCT | The evidence is very uncertain about the effect of hydroxychloroquine alone (6.7%) compared with standard treatment (6.7%) in 1 RCT (7). | Insufficient |
| *Rash* | 1 RCT | The evidence is very uncertain about the effect of hydroxychloroquine alone (3.2%) compared with standard treatment (0%) in 1 RCT (8). | Insufficient |
| *Headache* | 1 RCT | The evidence is very uncertain about the effect of hydroxychloroquine alone (3.2%) compared with standard treatment (0%) in 1 RCT (8). | Insufficient |
| *Anemia* | 1 RCT | The evidence is very uncertain about the effect of hydroxychloroquine alone (0%) compared with standard treatment (6.7%) in 1 RCT (7). | Insufficient |

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**Treatment**

**Evidence for Potential Harms**

| Outcome | Study Design | Evidence | Certainty of Evidence† |
|---|---|---|---|
| *Elevated serum creatinine* | 1 RCT | The evidence is very uncertain about the effect of hydroxychloroquine alone (0%) compared with standard treatment (6.7%) in 1 RCT (7). | Insufficient |
| **Hydroxychloroquine in combination with azithromycin for treatment of COVID-19** | | | |
| *Prolonged QTc interval* | 1 OBS | The QTc interval significantly increased (435 ± 24 ms at baseline to a maximal value of 463 ± 32 ms) in 1 case series study (13); however, a prolonged QTc interval was not reported for any patients in another case series study (16). | Insufficient |

**Evidence Gaps for COVID-19**

- Efficacy and safety of chloroquine used alone or in combination with azithromycin for prophylaxis or treatment of COVID-19 [no evidence].
- Efficacy and safety of hydroxychloroquine used alone or in combination with azithromycin for prophylaxis of COVID-19 infection [no evidence].
- Efficacy and safety of hydroxychloroquine used alone or in combination with azithromycin for treatment of patients with COVID-19 with varying severity of disease [insufficient evidence].
- Evaluation of important clinical outcomes including survival, respiratory failure, duration of mechanical ventilation, and use of ECMO [no evidence].

**Clinical Considerations**

- The use and extent of parallel treatment interventions, in addition to hydroxychloroquine alone or in combination with azithromycin, is difficult to determine.
- Known harms of chloroquine in patients without COVID-19 include (but not limited to): cardiovascular (cardiomyopathy, ECG changes), hematologic (aplastic anemia, thrombocytopenia), nervous system (seizures, psychosis, extrapyramidal disorders), ophthalmic macular degeneration) (5).
- Known harms of hydroxychloroquine in patients without COVID-19 include (but not limited to): cardiovascular (cardiomyopathy, cardiac failure, ventricular arrhythmias, torsade de pointes), endocrine (hypoglycemia), hematologic (aplastic anemia, thrombocytopenia), nervous system (seizures, psychosis, extrapyramidal disorders), ophthalmic macular degeneration) (6).
- Shared and informed decision making with a patient (and/or families) should include a discussion of potential harms of chloroquine and hydroxychloroquine and lack of known benefits in patients with COVID-19.
- In the evidence reviewed, hydroxychloroquine doses did not exceed 600 mg daily for 5 to 10 days.
- Chloroquine and hydroxychloroquine are used to manage other major ailments, such as rheumatic diseases, with a known benefit and are in short supply in the United States.
- Inappropriate and overuse of antibiotics (e.g., azithromycin) is an important contributor to the antibiotic resistance, an immediate public health threat (17).

CT = computed tomography; ECG = electrocardiography; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; OBS = observational study; PCR = polmerase chain reaction; RCT = randomized controlled trial.
Evidence search conducted by the University of Connecticut Health Outcomes, Policy, and Evidence Synthesis Group.
* Efficacy cannot be evaluated in case-series studies (16, 18).
† Certainty: insufficient, when confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its impact on a health outcome; low, confidence in the effect is limited as the true effect may be substantially different from the estimated effect; moderate, confidence in the effect is moderate as the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different; high, confident that the true effect is close to the estimated effect.

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**Note:** The Practice Points are developed by the Scientific Medical Policy Committee of the American College of Physicians. The Practice Points are "guides" only and may not apply to all patients and all clinical situations. All Practice Points are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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## Appendix: Practice Points Development Process

The Scientific Medical Policy Committee (SMPC), in collaboration with staff from ACP's Department of Clinical Policy, developed these Practice Points based on a rapid systematic evidence review conducted by the University of Connecticut Health Outcomes, Policy, and Evidence Synthesis Group. The SMPC comprises 11 internal medicine physicians representing various clinical areas of expertise and 1 public (nonclinician) member and includes members with expertise in epidemiology, healthy policy, and evidence synthesis. In addition to contributing clinical, scientific, and methodological expertise, Clinical Policy staff provided administrative support and liaised among the SMPC, evidence review funding entity and evidence team, and the journal. Clinical Policy staff and the SMPC reviewed and prioritized potential topic suggestions from ACP members, SMPC members, and ACP governance. A committee subgroup, including the chair of SMPC, worked with staff to draft the key questions and lead the development of the Practice Points. Clinical Policy staff worked with the subgroup and the evidence review team to refine the key question(s) and determine appropriate evidence synthesis methods for each key question. Via conference calls and e-mail, Clinical Policy staff worked with the committee subgroup to draft the Practice Points based on the results of the rapid systematic evidence review. The full SMPC reviewed and approved the final Practice Points. Before publication, ACP's Executive Committee of the Board of Regents also reviewed and approved the Practice Points on behalf of the ACP Board of Regents. The evidence review will be continually updated by the evidence review team. ACP will update the Practice Points based on the evidence review using the same process as for Version 1 (described above).