

UPDATE ALERTS

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 2)

In this letter, we update the American College of Physicians' previous practice points about chloroquine or hydroxychloroquine alone or in combination with azithromycin for prophylaxis or treatment of coronavirus disease 2019 (COVID-19) (1), using an updated evidence review conducted on 8 May 2020 (2). The evidence update identified 6 new studies: 4 observational studies (3–6) addressed use of hydroxychloroquine alone, 1 observational study (7) focused on hydroxychloroquine alone and in combination with azithromycin, and 1 observational study (8) assessed use of chloroquine alone (previously, no studies were available on the use of chloroquine alone). All new studies evaluated use of the pharmacologic interventions for treatment of COVID-19. The new evidence added support to previous conclusions but resulted in no conceptual changes to the practice points (see the next section and the Table). The Supplement summarizes the evidence, evidence gaps, and clinical considerations.

Practice Points: These interim practice points are based on the best available evidence. We will maintain these practice points as a living guidance document that will be updated as new evidence becomes available.

- Do not use chloroquine or hydroxychloroquine alone or in combination with azithromycin as prophylaxis against COVID-19.

- Do not use chloroquine or hydroxychloroquine alone or in combination with azithromycin as a treatment of patients with COVID-19.

- Clinicians may choose to treat hospitalized COVID-19-positive patients with chloroquine or hydroxychloroquine alone or in combination with azithromycin in the context of a clinical trial, using shared and informed decision making with patients (and their families).

Rationale for Prophylaxis: There continues to be no available evidence about the benefits and harms of use of chloroquine or hydroxychloroquine alone or in combination with azithromycin for prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, both chloroquine and hydroxychloroquine are associated with harms in patients without COVID-19. In the absence of evidence in patients with COVID-19, the risk for known harms in patients without COVID-19 outweighs the potential of any unknown benefit to prevent SARS-CoV-2 infection.

Rationale for Treatment: The evidence remains very uncertain about the benefits and harms of use of chloroquine or hydroxychloroquine alone or in combination with azithromycin for treatment of COVID-19, even with the new studies about the benefits and harms of chloroquine alone or hydroxychloroquine alone or in combination with azithromycin. There is still no available evidence about the benefits and harms of use of chloroquine in combination with azithromycin. Both chloroquine and hydroxychloroquine are associated

with harms in patients without COVID-19. In light of very uncertain evidence on the benefit for the treatment of COVID-19, the risk for known harms outweighs the potential for unknown benefit. However, clinicians may choose to treat hospitalized COVID-19-positive patients with chloroquine or hydroxychloroquine alone or in combination with azithromycin in the context of a clinical trial using shared and informed decision making with patients and their families. These hospitalized patients will need to be carefully and closely monitored for any potential harms.

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Table. Evidence Summary: What Information Does the Evidence Provide?***[NEW] indicates evidence that has been added since the previous version.**

Prophylaxis			
+ Evidence for Potential Benefits			
Chloroquine or hydroxychloroquine alone or in combination with azithromycin for prevention of COVID-19			
No studies identified			
- Evidence for Potential Harms			
Chloroquine or hydroxychloroquine alone or in combination with azithromycin for prevention of COVID-19			
No studies identified			
Treatment			
+ Evidence for Potential Benefits			
Outcome	Study Design	Evidence	Certainty of Evidence†
Chloroquine alone for treatment of COVID-19 [NEW]			
<i>Conversion of SARS-CoV-2 test result from positive to negative</i>	1 OBS (n = 373)	Very uncertain about the effect of chloroquine alone compared with standard treatment on the conversion to negative on day 10 and day 14 via viral RNA test from respiratory tract samples (8)	Insufficient
<i>All-cause mortality</i>	1 OBS (n = 373)	Very uncertain about the effect of chloroquine alone compared with standard treatment (8)	Insufficient
<i>Symptom resolution</i>	1 OBS (n = 373)	Very uncertain about the effect of chloroquine alone compared with standard treatment on resolution of fever (8)	Insufficient
<i>ICU admission</i>	1 OBS (n = 373)	Very uncertain about the effect of chloroquine alone compared with standard treatment (8)	Insufficient
Chloroquine in combination with azithromycin for treatment of COVID-19			
No studies identified			
Hydroxychloroquine alone for treatment of COVID-19			
<i>Conversion of SARS-CoV-2 test result from positive to negative</i>	2 RCTs (n = 180)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on the conversion to negative on day 7 or day 14 via throat swab, sputum, or lower respiratory tract secretion (9) and hydroxychloroquine alone compared with standard treatment up to day 23 via upper and/or lower respiratory tract specimens or the time to negative results (10)	Insufficient
	2 OBSs (n = 70)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on the conversion to negative via nasopharyngeal PCR on day 6 (11) and [NEW] day 14 (4)	
<i>Progression of pulmonary lesions on CT scan</i>	2 RCTs (n = 92)	Hydroxychloroquine alone may not reduce the progression or exacerbation of pulmonary lesions on CT scan compared with standard treatment (9, 12)	Low
<i>Improvement in pulmonary lesions on CT scan</i>	1 RCT (n = 62)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on radiologic improvement of pneumonia (12)	Insufficient
<i>Symptom resolution</i>	3 RCTs (n = 242)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment for resolution of fever (9, 12); cough (12); and fever, respiratory symptoms, and oxygenation (10)	Insufficient
<i>Severe disease progression</i>	2 RCTs (n = 242)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (9, 12)	Insufficient
	3 OBS (n = 277)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment to reduce the level of respiratory support (13) or prevent the development of acute respiratory distress syndrome (14) or [NEW] need for high-flow oxygen (4)	
<i>All-cause mortality [NEW STUDIES ADDED]</i>	1 RCT (n = 30)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (9)	Insufficient
	7 OBSs (n = 2756)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (3-7, 13, 14)	
<i>Composite of intubation or death [NEW]</i>	1 OBS (n = 1376)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (3)	Insufficient
<i>Need for mechanical ventilation [NEW]</i>	3 OBSs (n = 1778)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (3, 4, 7)	Insufficient
<i>Composite of ICU admission within 7 days or death</i>	1 OBS (n = 181)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on transfer to the ICU within 7 days and/or death from any cause (14)	Insufficient

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Table—Continued

[NEW] indicates evidence that has been added since the previous version.

Hydroxychloroquine in combination with azithromycin for treatment of COVID-19 [NEW]			
<i>All-cause mortality</i>	1 OBS (n = 368)	Very uncertain about the effect of hydroxychloroquine in combination with azithromycin compared with standard treatment (7)	Insufficient
<i>Need for mechanical ventilation</i>	1 OBS (n = 368)	Very uncertain about the effect of hydroxychloroquine in combination with azithromycin compared with standard treatment (7)	Insufficient
<i>Discharge from hospital</i>	1 OBS (n = 368)	Very uncertain about the effect of hydroxychloroquine in combination with azithromycin compared with standard treatment (7)	Insufficient
⊖ Evidence for Potential Harms			
Outcome	Study Design	Evidence	Certainty of Evidence†
Chloroquine alone for treatment of COVID-19 [NEW]			
<i>Any adverse events</i>	1 OBS (n = 373)	Very uncertain about the effect of chloroquine alone compared with standard treatment (8)	Insufficient
<i>Diarrhea</i>	1 OBS (n = 373)	Very uncertain about the effect of chloroquine alone compared with standard treatment (8)	Insufficient
<i>Rash</i>	1 OBS (n = 373)	Very uncertain about the effect of chloroquine alone compared with standard treatment (8)	Insufficient
<i>Headache</i>	1 OBS (n = 373)	Very uncertain about the effect of chloroquine alone compared with standard treatment (8)	Insufficient
Chloroquine in combination with azithromycin for treatment of COVID-19			
No studies identified			
Hydroxychloroquine alone for treatment of COVID-19			
<i>Severe adverse events</i>	1 RCT (n = 62)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (12)	Insufficient
<i>Any adverse event</i>	3 RCTs (n = 242)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment on adverse effects (9, 10, 12)	Insufficient
<i>Severe prolonged QTc interval (>500 ms)</i>	1 OBS (n = 181)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (14)	Insufficient
<i>Prolonged QTc interval</i>	1 OBS (n = 181)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (14)	Insufficient
<i>Diarrhea</i>	2 RCTs (n = 180)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (9, 10)	Insufficient
<i>Abnormal liver function</i>	1 RCT (n = 30)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (9)	Insufficient
<i>Rash</i>	1 RCT (n = 62)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (12)	Insufficient
<i>Headache</i>	1 RCT (n = 62)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (12)	Insufficient
<i>Anemia</i>	1 RCT (n = 30)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (9)	Insufficient
<i>Elevated serum creatinine level</i>	1 RCT (n = 30)	Very uncertain about the effect of hydroxychloroquine alone compared with standard treatment (9)	Insufficient
Hydroxychloroquine in combination with azithromycin for treatment of COVID-19			
No studies identified			

COVID-19 = coronavirus disease 2019; CT = computed tomography; ICU = intensive care unit; OBS = observational study; PCR = polymerase chain reaction; RCT = randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* The evidence search was conducted by the University of Connecticut Health Outcomes, Policy, and Evidence Synthesis Group. See Supplement Table 3 for data estimates.

† Certainty of evidence is graded as insufficient (confidence is inadequate to assess the likelihood of benefit [benefit minus harm] of an intervention or its effect on a health outcome), low (confidence in the effect is limited because the true effect may be substantially different from the estimated effect), moderate (confidence in the effect is moderate because the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different), or high (confidence that the true effect is close to the estimated effect).

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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