

## UPDATE ALERT

**Update Alert 3: Hydroxychloroquine or Chloroquine for the Treatment or Prophylaxis of COVID-19**

This report, the third update of a previously published living systematic review (1), focuses on treatment (not prophylaxis) of coronavirus disease 2019 (COVID-19) with hydroxychloroquine or chloroquine. The first and second updates covered evidence available through 1 July 2020 (2) and 1 August 2020 (3), respectively. This update evaluates evidence published through 21 September 2020.

No new evidence about chloroquine was found. One new randomized trial (4) and 5 new cohort studies (5-9) evaluating hydroxychloroquine were found. None of the studies used zinc; all studies (5-8) except for 1 (9) with a hydroxychloroquine group and an azithromycin group evaluated hydroxychloroquine alone. The trial used a "standard care" control group (4) and had high risk of bias, whereas all of the cohort studies had serious risk of bias (5-9). The trial (4) and 3 of the new cohort studies (6, 7, 9) assessed hospital-initiated hydroxychloroquine, whereas 2 of the new cohort studies (5, 8) assessed prehospital initiation.

The **Supplement Table** displays the following for outcomes of all identified trials (4, 10-16, 32, 34) and cohort studies (5-9, 17-31, 33, 35) that addressed treatment with hydroxychloroquine: risk-of-bias assessments, unadjusted estimates of effect, and overall ratings of strength of evidence. In trials, when hydroxychloroquine is initiated in the outpatient setting, there is low strength of evidence that it reduces hospitalizations (11, 12); whereas, in cohort studies, there remains insufficient evidence (5, 8, 33). There is now low strength of evidence that hydroxychloroquine has no positive effect on all-cause mortality and need for mechanical ventilation in both trials and cohort studies. Even with 3 new cohort studies assessing intensive care unit admission (5, 6, 8) and 1 trial (4) and 1 cohort study (9) assessing symptom resolution, there is still insufficient evidence for determining hydroxychloroquine's effect on both outcomes. No new trial or studies assessed any other outcome.

It is becoming increasingly unlikely that in-hospital use of hydroxychloroquine will yield beneficial effects. The large SOLIDARITY-WHO and ORCHID-NIH trials have been prematurely discontinued, with press releases citing lack of efficacy (36, 37), but preprints or publications of these trials are still not available. However, the outpatient use of hydroxychloroquine is more promising. Trials with some concern of bias (11) and high risk of bias (12) found nonsignificant reductions in hospitalizations, whereas 2 cohort studies with serious risk of bias found significant reductions (5, 8). However, 1 cohort study with critical risk of bias found a significant increase (33). One of these cohort studies (5) found a significant reduction in intensive care unit admission with hydroxychloroquine use, whereas another found a nonsignificant reduction (8), which is in contrast to 2 cohort studies (6, 24) with serious risk of bias assessing inpatient use of hydroxychloroquine where intensive care unit admissions were significantly increased.

Adrian V. Hernandez, MD, PhD

University of Connecticut Health Outcomes, Policy, and Evidence Synthesis Group and Hartford Hospital Department of Research Administration, Hartford, Connecticut School of Pharmacy, Storrs, Connecticut and Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima, Peru

Yuani M. Roman, MD, MPH

University of Connecticut Health Outcomes, Policy, and Evidence Synthesis Group and Hartford Hospital Department of Research Administration, Hartford, Connecticut

Vinay Pasupuleti, MD, MS, PhD

MedErgy HealthGroup, Yardley, Pennsylvania

Joshuan J. Barboza, MSc

Vicerrectorado de Investigación, Universidad San Ignacio de Loyola, Lima, Peru

C. Michael White, PharmD

University of Connecticut Health Outcomes, Policy, and Evidence Synthesis Group and Hartford Hospital Department of Research Administration, Hartford, Connecticut, and School of Pharmacy, Storrs, Connecticut

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**Corresponding Author:** C. Michael White, PharmD, University of Connecticut School of Pharmacy, 69 North Eagleville Road, U-3092, Storrs, CT 06269; e-mail, [charles.white@uconn.edu](mailto:charles.white@uconn.edu).

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