

UPDATE ALERT

Update Alert 2: 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

This letter serves to retire the American College of Physicians' (ACP) rapid, living practice points on the use chloroquine or hydroxychloroquine alone or in combination with azithromycin for the prophylaxis or treatment of coronavirus disease 2019 (COVID-19) (1, 2) from the living status. This decision was made in light of recent information on the topic. Three large, in-progress randomized controlled trials (RCTs) with strong study designs ceased enrollment for the hydroxychloroquine-only versus control comparison early due to lack of efficacy in preliminary analyses (3-5). In addition, the 2 literature updates produced no evidence to alter these conclusions. The U.S. Food and Drug Administration also recently revoked its emergency use authorization for chloroquine and hydroxychloroquine for the treatment of COVID-19 due to potential significant harms and lack of benefits (6). The ACP's Scientific Medical Policy Committee (SMPC) has determined that the emergence of new evidence is unlikely to change the existing practice points; therefore, regularly scheduled updates are no longer warranted. The SMPC will continue to review the planned ongoing surveillance through November 2020 (7). The updated evidence review (8) identified 1 new RCT (9); 5 new cohort studies (10-14); and complete published reports of studies previously available as preprints, which resulted in changes in rating of the risk of bias (15, 16). A sixth newly published large cohort study was identified but not considered further because it was retracted due to concerns about the veracity of the data (17, 18). The newly available evidence has high risk of bias and showed conflicting direction and magnitude of results, leading to unchanged conclusions from the initial review with insufficient evidence to support the effectiveness or safety of chloroquine or hydroxychloroquine alone or in combination with azithromycin for the treatment of COVID-19 in hospitalized patients. Furthermore, 3 RCTs were stopped early (3-5) and no data were available to assess from those RCTs.

Practice Points

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).

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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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References

- Qaseem A, Yost J, Etxeandia-Ikobaltzeta I, et al. 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). *Ann Intern Med.* 2020;173:137-142. [PMID: 32422063] doi:10.7326/M20-1998
- Qaseem A, Yost J, Etxeandia-Ikobaltzeta I, et al. Update alert: 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 [Letter]. *Ann Intern Med.* 2020; 173:W48-W51. [PMID: 32551892] doi:10.7326/M20-3862
- RECOVERY trial. No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19: statement from the chief investigators of the randomised evaluation of covid-19 therapy (RECOVERY) trial on hydroxychloroquine. 5 June 2020. Accessed at www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19 on 6 July 2020.

4. World Health Organization. WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19 [news release]. 4 July 2020. Accessed at www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19 on 6 July 2020.
5. National Institutes of Health. NIH halts clinical trial of hydroxychloroquine: study shows treatment does no harm, but provides no benefit [news release]. 20 June 2020. Accessed at www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine on 6 July 2020.
6. U.S. Food and Drug Administration. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine [news release]. 15 June 2020. Accessed at www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and on 16 July 2020.
7. Hernandez AV, Roman YM, Pasupuleti V, et al. Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19: A living systematic review. *Ann Intern Med.* 2020. [PMID: 32459529] doi:10.7326/M20-2496
8. Hernandez AV, Roman YM, Pasupuleti V, et al. Update alert: hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19 [Letter]. *Ann Intern Med.* 2020. [PMID: 32667853] doi:10.7326/L20-0945
9. Chen L, Zhang ZY, Fu JG, et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. *medRxiv.* Preprint posted online 22 June 2020. doi:10.1101/2020.06.19.20136093
10. Sbidian E, Josse J, Lemaitre G, et al. Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France. *medRxiv.* Preprint posted online 19 June 2020. doi:10.1101/2020.06.16.20132597
11. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in new york state. *JAMA.* 2020. [PMID: 32392282] doi:10.1001/jama.2020.8630
12. Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients—an observational study. *medRxiv.* Preprint posted online 25 May 2020. doi:10.1101/2020.05.21.20109207
13. Singh S, Khan A, Chowdhry M, et al. Outcomes of hydroxychloroquine treatment among hospitalized COVID-19 patients in the United States—real-world evidence from a federated electronic medical record Network. *medRxiv.* Preprint posted online 19 May 2020. doi:10.1101/2020.05.12.20099028
14. Arshad S, Kilgore P, Chaudhry ZS, et al; Henry Ford COVID-19 Task Force. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis.* 2020;97:396-403. [PMID: 32623082] doi:10.1016/j.ijid.2020.06.099
15. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ.* 2020;369:m1849. [PMID: 32409561] doi:10.1136/bmj.m1849
16. Yu B, Li C, Chen P, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. *Sci China Life Sci.* 2020. [PMID: 32418114] doi:10.1007/s11427-020-1732-2
17. Rosenthal M. 2 papers about drug therapy for COVID-19 retracted from prestigious journals. *Pharmacy Practice News.* 4 June 2020. Accessed at www.pharmacypracticenews.com/Covid-19/Article/05-20/2-Papers-About-Drug-Therapy-in-COVID-19-Retracted-From-Prestigious-Journals/58677 on 6 July 2020.
18. Mehra MR, Desai SS, Ruschitzka F, et al. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet.* 2020. [PMID: 32450107] doi:10.1016/S0140-6736(20)31180-6