

Avoidance of hydroxychloroquine in outpatient settings

To date randomized clinical trials have failed to demonstrate benefit with hydroxychloroquine compared to standard of care or placebo for treatment or prevention of mild to moderate and severe COVID-19 among patients in the outpatient and inpatient settings. Use of hydroxychloroquine is not recommended due to lack of efficacy compared to standard of care as well as concern for potential adverse events.

- **Current expert recommendations:**
 - NIH: **Recommends against** use of hydroxychloroquine (HCQ) or chloroquine for treatment of COVID-19, particularly outside of a hospital, except in clinical trial¹
 - **Recommends against** HCQ plus azithromycin, except in clinical trial
 - WHO: Recommends that HCQ (+/- azithromycin) **should not be administered as treatment nor prophylaxis** for COVID-19, outside of clinical trials²
 - IDSA: **Suggests against** HCQ plus azithromycin outside of clinical trials³
 - FDA: **Cautions against use** of HCQ for COVID-19 outside of hospital or clinical trial due to risk of arrhythmias⁴
 - Revoked emergency use authorization (EUA) based on evidence demonstrating no benefit for decreasing likelihood of death nor speeding recovery
 - American College of Physicians: **Should not use** hydroxychloroquine alone or in combination with azithromycin for COVID-19 due to known harms and no available of evidence of benefit⁵
 - Northwestern Medicine ASP/ID Division: **Not recommended** for COVID-19 due to lack of definitive evidence differentiating outcomes benefit with HCQ compared to supportive care and increased risk of adverse events⁶
- Adverse events:
 - QTc prolongation, ventricular arrhythmia, cardiac death, drug-drug interactions, hypoglycemia
- Select evidence (see supporting evidence document for individual trial details):

Setting/Severity	Findings/Strength	References
Treatment for outpatients with mild/moderate COVID-19	Two randomized trials did not demonstrate benefit of symptom improvement nor reduction of viral load in patients receiving HCQ compared to placebo or no antiviral treatment (n=716 patients)	7, 8
Treatment for hospitalized patients with mild/moderate COVID-19	Two randomized trials observed no improvement in clinical status nor rate of negative viral conversion among those patients receiving HCQ compared to standard of care (n=654 patients)	9, 10
Treatment for hospitalized patients with severe COVID-19	RECOVERY randomized trial did not demonstrate mortality difference in patients receiving HCQ compared to usual care (n=4716 patients) Observational non-randomized study demonstrating HCQ benefit confounded by disproportional rates of steroid use, ICU-level care, and mechanical ventilation among those receiving HCQ compared to those who did not	11, 12
Post-exposure prophylaxis	Two randomized trials demonstrated no benefit in preventing development of confirmed or probable COVID-19 in high-risk groups receiving HCQ compared to placebo or no therapy (n=3135 patients)	13, 14

References:

1. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19treatmentguidelines.nih.gov/>.
2. Clinical management of COVID-19. World Health Organization. Updated 27 May 2020. Available at <https://www.who.int/publications/i/item/clinical-management-of-covid-19>
3. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America. Available at <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>
4. Press Release: FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. U.S. Food and Drug Administration. 1 July 2020. Available at <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or>
5. Qaseem A 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;173:137-143.
6. Northwestern Medicine ASP Evidence Review for Inpatient Treatment Options for COVID-19. Last Updated 8 August 2020. Available at https://asp.nm.org/uploads/9/0/7/8/90789983/nm_asp_covid-19_treatment_evidence_review_8.5.20.pdf
7. Skipper CP et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. A randomized trial. *Ann Intern Med.* 2020. DOI: [10.7326/M20-4207](https://doi.org/10.7326/M20-4207)
8. Mitjà O et al. Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial, *Clinical Infectious Diseases*, Available at <https://academic.oup.com/cid/doi/10.1093>.
9. Calvacanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *New Engl J Med*, 2020. DOI: [10.1056/NEJMoa2019014](https://doi.org/10.1056/NEJMoa2019014)
10. 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 DOI: <https://doi.org/10.1136/bmj.m1849>
11. Pre-print: Horby P et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRxiv. 15 July 2020. DOI: <https://doi.org/10.1101/2020.07.15.20151852>
12. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with Hydroxychloroquine, Azithromycin and a Combination in Patients Hospitalized with COVID-19. *Int J Infect Dis* 2020. [https://www.ijidonline.com/article/S1201-9712\(20\)30534-8/fulltext](https://www.ijidonline.com/article/S1201-9712(20)30534-8/fulltext)
13. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *New Engl J Med*, 2020. <https://doi.org/10.1056/NEJMoa2016638>
14. Pre-print: Mitja O et al. A Cluster-Randomized Trial of Hydroxychloroquine as Prevention of Covid-19 Transmission and Disease. medRxiv. 26 July 2020. DOI: <https://doi.org/10.1101/2020.07.20.20157651>