COVID-19: PROPHYLACTIC USE OF HYDROXYCHLOROQUINE (HCQ)

A Rapid Guidance Summary from the Penn Medicine Center for Evidence-based Practice
Last updated July 1, 2020. All links rechecked June 30 unless otherwise noted.

This Rapid Guidance Summary is a description of existing guidance and evidence reviews from a variety of sources that was in effect at the time of publication. It should not be used or interpreted as a clinical practice guideline, but instead can be used in development of local recommendations and policies.

Key questions answered in this summary

- Is hydroxychloroquine effective for prevention of clinical disease in patients who have been exposed to SARS-CoV-2?

  Use of hydroxychloroquine for treatment of confirmed COVID-19 disease is outside the scope of this report.

Summary of major recommendations

- Use of hydroxychloroquine or chloroquine for prevention of COVID-19 disease is not recommended outside of approved clinical trials.
- A systematic review of clinical evidence found only one trial evaluating HCQ for preventing COVID-19 disease in persons with history of exposure to infected patients. Results of that single trial did not demonstrate reduced COVID-19 disease with hydroxychloroquine, and the risk of adverse events is possibly increased. The risk of bias in that study was high.
- There are no medical centers using hydroxychloroquine or chloroquine for prevention of COVID-19 disease outside of approved clinical trials.

Recent public health agency and professional society guidelines on prophylactic use of hydroxychloroquine

Source	Recommendations
Public health agencies	
FDA June 15	The Emergency Use Authorization for hydroxychloroquine (now withdrawn) applied only to patients hospitalized with COVID-19 disease; prophylactic use was never authorized.
WHO May 27	We recommend that chloroquine and hydroxychloroquine (± azithromycin) not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials.
Professional societies	
ACP June 30	The American College of Physicians specifically does not recommend use of chloroquine or hydroxychloroquine alone or in combination with azithromycin as prophylaxis against COVID-19.
Australia June 17	For people exposed to individuals with COVID-19, only administer hydroxychloroquine for post-exposure prophylaxis in the context of randomized trials with appropriate ethical approval.
ACOEM June 17	Hydroxychloroquine and chloroquine are not recommended for use for widespread prophylaxis against COVID-19. Strength of evidence: not recommended, insufficient evidence. Level of confidence: low.

CEP NOTE: NIH guidelines do not apply to prophylaxis in persons with SARS-CoV-2 exposure

Systematic reviews with quantitative data synthesis

Source	Findings
Living Evidence June 30	For outcome of positive COVID-19 disease within 14 days of exposure to infected person: Summary risk ratio 0.83, 95% CI 0.58-1.18, p = 0.30, I_2 not applicable, 1 trial, 821 patients, moderate risk of bias. For outcome of adverse events: Summary risk ratio 2.39, 95% CI 1.83-3.11, p < 0.001, I_2 not applicable, 1 trial, 701 patients, high risk of bias. *CEP NOTE: Please see linked page for current review results including forest plots of results.*

CEP NOTE: The protocol for a Cochrane Review on this topic has been published, but the review is not yet completed.

Other recent evidence reviews on prophylactic use of hydroxychloroquine

Source	Findings
ACP June 30	A randomized trial of hydroxychloroquine for postexposure prophylaxis within 4 days after high-risk or moderate-risk exposure to Covid-19 showed no prevention of Covid-19 or compatible illness, although most patients did not start therapy for at least 3 days after SARS-CoV-2 exposure
EM-RAP June 30	A recent randomized, double-blind, placebo-controlled trial of hydroxychloroquine as post-exposure prophylaxis after a high risk exposure to COVID-19 did not show any clinical benefit. The majority of subjects enrolled (87.6%) had a high risk exposure defined as being less than 6 feet from someone with confirmed COVID-19 without a face mask or eye shield for greater than 10 minutes. Subjects were randomized to HCQ 800 mg orally once followed by 600 mg daily x 4 days vs placebo. There was no significant difference in the development of confirmed or probable COVID-19 in the HCQ group vs placebo (11.8% vs 14.3%, p = 0.35). There were more side effects, predominantly gastrointestinal in nature, in the hydroxychloroquine group.
CEBM June 27	On 26 June the UK Medicines and Healthcare products Regulatory Agency announced that it had "given the [COPCOV] clinical trial the green light to recruit more participants at the request of the COPCOV trialists, who are studying the use of hydroxychloroquine in preventing COVID-19. At the same time, MHRA reminded prescribers that "Chloroquine and hydroxychloroquine are not licensed to treat COVID-19 related symptoms or prevent infection" and that "until we have clear, definitive evidence that these treatments are safe and effective for the treatment of COVID-19, they should only be used for this purpose within a clinical trial."
Southern Cal. June 26	Major media outlets have reported hydroxychloroquine does not prevent COVID-19. This is based on a randomized, double-blind placebo controlled trial of 821 asymptomatic participants in which the investigators concluded there was no difference in the incidence of new illness between placebo and hydroxychloroquine. Some have argued, however, the study may not be definitive, because the participants self-reported symptoms and there was no testing, raising the question of the trial design.
ASHP June 25	Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 is not established. No data to date indicating that in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Only limited clinical trial data available to date to evaluate use of hydroxychloroquine for prevention of COVID-19.
Brigham June 23	The first randomized control trial for COVID-19 post-exposure prophylaxis was published on June 3, 2020. Asymptomatic patients who had household or occupational exposures to others with COVID-19 for more than 10 minutes within 4 days of exposure were randomized to receive either placebo (n=407) or hydroxychloroquine 800 mg once, 600 mg in 6-8 hours, then 600 mg daily for 4 additional days (n=414). The incidence of new illness compatible with COVID-19 was 11.8% in the hydroxychloroquine arm and 14.3% in the placebo arm (absolute difference -2.4%, 95% CI -7 to 2.2%, p=0.35). Side effects were more common in the hydroxychloroquine arm (40.1% vs. 16.8%), but no serious adverse reactions were reported.
SIDP June 15	Role for post-exposure prophylaxis is not compelling, at least among clinical/healthcare worker exposures
Washington June 9	A double-blind placebo-controlled RCT found that prophylactic hydroxychloroquine fails to prevent symptomatic infection after SARS-CoV-2 exposure.

Medical center guidance on prophylactic use of hydroxychloroquine

Hospital	Policy/recommendation
Mass. General June 24	There is currently no proven role for post exposure prophylaxis for healthcare workers with a known COVID-19 exposure. No benefit of hydroxychloroquine was seen in a double-blinded placebo randomized controlled trial.
Brigham June 23	Hydroxychloroquine is not recommended outside of the context of a clinical trial.
Penn Medicine June 20	We do not recommend routine post-exposure prophylaxis.

Guidance sources

ACOEM- American College of Occupational and Environmental Medicine
ACP–American College of Physicians
ASHP–American Society of Health System Pharmacists
CEBM–University of Oxford Centre for Evidence-based Medicine
EM-RAP–Emergency Medicine Reviews and Perspectives
Living Evidence–an ad hoc collaboration of Cochrane Collaboration members and hospital health technology assessment specialists
SIDP–Society of Infectious Disease Pharmacists

Update history

July 1: Updated ACP and medical center guidance. Outdated guidance removed. New section for systematic reviews, other evidence reviews updated. Conclusions strengthened.
April 21: Updated evidence reviews and medical center guidance.
April 11: Initial report.

About this report

A Rapid Guidance Summary is a focused synopsis of recommendations from selected guideline issuers and health care systems, intended to provide guidance to Penn Medicine providers and administrators during times when latest guidance is urgently needed. It is not based on a complete systematic review of the evidence. Please see the CEP web site for further details on the methods for developing these reports.

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