COVID-19: TREATMENT WITH HYDROXYCHLOROQUINE (HCQ)

A Rapid Guidance Summary from the Penn Medicine Center for Evidence-based Practice
Last updated June 26, 2020. All links rechecked June 26 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 safe and effective for treatment of COVID-19 disease?
  Use of hydroxychloroquine for prevention of COVID-19 disease is outside the scope of this report.

Summary of major recommendations

- The FDA has withdrawn Emergency Use Authorization for hydroxychloroquine in COVID-19 disease, but clinical trials remain in progress.
- Systematic reviews of clinical evidence show little to no benefit, and possible harms from use of hydroxychloroquine for treatment of COVID-19 disease (GRADE strength of evidence evaluation: very low).
- The most recent guidance from professional societies recommends against use of hydroxychloroquine treatment of COVID-19 disease.
- Medical center guidelines do not recommend use of HCQ outside of clinical trials.

Recent public health agency and professional society guidelines on hydroxychloroquine for treatment of COVID-19 disease

Source	Recommendations
Public health agencies	
NIH June 16	The Panel recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (strong recommendation, based on non-randomized studies).
FDA June 15	The Emergency Use Authorization issued on March 28 has been withdrawn. Based on its ongoing analysis of the EUA and emerging scientific data, the FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use. Ongoing clinical trials are allowed to continue. Treatment of COVID-19 patients who have already been given hydroxychloroquine is allowed to continue.
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 26	ACP advises against use of chloroquine or hydroxychloroquine alone or in combination with azithromycin as treatment for COVID-19, and recommends shared and informed decision making if hospitalized patients are treated with either drug alone or in combination with azithromycin in the context of a clinical trial.
IDSA June 25	Among patients with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine only in the context of a clinical trial. (Knowledge gap) Among patients with COVID-19, the IDSA guideline panel suggests against hydroxychloroquine/chloroquine plus azithromycin outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

Source	Recommendations
Australia June 24	Not recommended. For people with COVID-19, only administer hydroxychloroquine in the context of randomized trials with appropriate ethical approval. The Taskforce is continually monitoring research on antiviral and other disease-modifying treatments. As evidence accumulates the Taskforce will continue to review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease). Several cohort studies exploring harms have been published and we are currently assessing the evidence. One study has subsequently been retracted [29] and is not being considered by the Taskforce.

Systematic reviews with quantitative data synthesis

Source	Findings
Living Evidence June 26	For outcome of viral negative status within 7 days: summary risk ratio 0.93, 95% CI 0.73-1.18, p = NS, I_2 not applicable, 1 trial, 30 patients, moderate risk of bias, evidence grade very low. (no significant difference) For outcome of adverse events within 14-28 days: summary risk ratio 2.73, 95% CI 1.49-5.01, p < 0.05 , I_2 = 0%, 3 trials, 210 patients, moderate risk of bias, evidence grade low. (increased adverse events with HCQ) Insufficient evidence for conclusions on other outcomes, including mortality. *CEP NOTE: Please see linked page for current review results including forest plot of results.*
IDSA June 22	Mortality risk: no significant difference (insufficient events to permit meta-analysis). Clinical progression within 3-6 days by CT: summary risk ratio 0.61, 95% CI 0.26 to 1.43, p = NS, I_2 not significant, 2 trials, 92 patients. (less progression with hydroxychloroquine, but result not statistically significant) Clinical improvement at 6 days by CT: summary risk ratio 1.45, 95% CI 1.02 to 2.11, p < 0.05, 1 trial, 62 patients, (more improvement with hydroxychloroquine) Failure of viral clearance at 7 days by PCR: summ. RR 2.00, 95% CI 0.20-20.0, p = NS, 1 trial, 30 patients. (more failure with hydroxychloroquine, but result not statistically significant) Any adverse events: summary risk ratio 3.14, 95% CI 1.58 to 6.24, p < 0.05, I_2 not signif., 2 trials, 242 patients. (significantly more adverse events with hydroxychloroquine) Evidence grade very low for all outcomes. A total of 3 RCTs and 6 cohort studies were found.
Patel et al. June 9	For outcome of mortality: hydroxychloroquine vs. usual care: summary odds ratio 1.25, 95% CI 0.65-2.38, p = 0.51, I_2 = 80%, 6 studies (all observational), 2,908 patients. For outcome of mortality: hydroxychloroquine + azithromycin vs. usual care: summary odds ratio 2.54, 95% CI 1.63-3.34, p < 0.001, I_2 = 0%, 3 studies (all observational), 1,249 patients. *CEP NOTE: Though the authors did not assess the strength of evidence, we would give it a grade of "very low."*

Other recent evidence reviews on hydroxychloroquine for treatment of COVID-19 disease

CEP NOTE: the protocol for a Cochrane Review on chloroquine and hydroxychloroquine for prevention and treatment of COVID-19 has been published, but the review is not yet complete.

Source	Findings
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 treatment or prevention of COVID-19. Clinical experience in treating pts with COVID-19: Majority of data to date involves use in pts with mild or moderate COVID-19; only limited clinical data on use in pts with severe and critical disease. Optimal dose and duration not known.

Source	Findings
	Additional data needed from randomized controlled trials before any conclusions can be made regarding possible benefits and safety of using hydroxychloroquine with azithromycin. Additional data needed regarding toxicity profile when used in patients with COVID-19
Australia June 24	Evidence informing this recommendation comes from three randomised trials that compared hydroxychloroquine sulfate plus standard care to standard care alone Two studies focused on patients experiencing moderate illness and one on patients with mild, moderate and severe illness. Each study was limited in the number of relevant outcomes reported All three reported the number of individuals experiencing one or more adverse events (two studies reported the incidence of severe adverse events and virological clearance at day 7 after treatment initiation , one study reported mortality) None reported the incidence of respiratory failure/ARDS or requirement for mechanical ventilation/ECMO The certainty of evidence for all reported outcomes is deemed to be very low This judgement is based on: serious risk of bias due to unclear reporting of sequence generation and allocation concealment and lack of blinding of patients and personnel ; and very serious imprecision due to the low number of patients and/or low number of observed events The exception was adverse events, in which certainty was low due to serious risk of bias and imprecision According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold Long term harms of relevance include retinopathy and chronic cardiac myopathy There are several known and potential interactions with other drugs Overdose of hydroxychloroquine may have potentially fatal complications Children are particularly at risk for overdose In pregnancy, it is only recommended when benefits outweigh harms Hydroxychloroquine is contraindicated if breastfeeding Based on the available evidence, there remains significant uncertainty whether hydroxychloroquine/chloroquine is more effective and safer than standard care in treating patients with COVID-19.
Brigham June 23	Hydroxychloroquine was found to be more potent than chloroquine in inhibiting SARS-CoV-2 in vitro. An expert consensus group out of China suggested that chloroquine improved lung imaging and shortened disease course. Chloroquine is included in the treatment guidelines from the National Health Commission of the People's Republic of China, but the specific data on which this is based is not available. One pre-print report of 62 COVID-19+ patients showed improved time to clinical recovery in the hydroxychloroquine treatment arm compared to placebo. However, a number of additional reports have since shown no positive impact with the addition of hydroxychloroquine
Penn Medicine June 20	Evidence of efficacy and/or effectiveness Mixed evidence of efficacy against SARSCoV-2 from three small randomized clinical trials in China. Among 62 patients (31 treated with hydroxychloroquine) hydroxychloroquine was associated with decreased duration of fever and cough.(Chen et al., 2020) However, among 150 patients with predominantly mild to moderate disease, there was no difference in median time to alleviation of symptoms.(Tang et al., 2020) Prospective observational study among 201 patients treated chloroquine/hydroxychloroquine + azithromycin demonstrated greater QT prolongation in the combination therapy group, however these events did not lead to torsades de pointes or death.(Saleh et al., 2020) Two observational studies found significantly lower mortality among patients receiving hydroxychloroquine compared to standard of care. Multiple clinical trials are ongoing. Limitations of evidence Limited clinical data. Two randomized trials among 30 patients (15 treated with hydroxychloroquine) and 150 patients (75 treated with hydroxychloroquine) found no difference in viral clearance between treatment and control.(Chen, 2020; Tang et al., 2020) A retrospective observational study among 368 male VA patients (97 receiving hydroxychloroquine) found increased risk of mortality among patients receiving hydroxychloroquine.(Magagnoli et al., 2020) Three observational studies found no difference in risk of intubation, ICU transfer, and/or death with hydroxychloroquine.(Geleris et al., 2020; Mahevas et al., 2020; Rosenberg et al., 2020) Prospective case report among 11 hospitalized patients with severe COVID-19 found no clinical benefit.(Molina et al., 2020)

Source	Findings
	Multiple studies reported adverse events among patients receiving hydroxychloroquine, including diarrhea, ECG changes, and rash (Litaiem, et al., 2020; Mahevas et al., 2020; Tang et al., 2020) A retrospective analysis evaluating the safety of chloroquine and hydroxychloroquine using reports from the FDA Adverse Event Reporting System pharmacovigilance database demonstrated that hydroxychloroquine has a safer clinical profile compared to chloroquine.(Papazisis et al., 2020) Retrospective study among 90 patients found QT prolongation associated with hydroxychloroquine, with greater prolongation among patients receiving combination hydroxychloroquine + azithromycin (n=53) compared to those receiving hydroxychloroquine alone (n=36).(Mercuro et al., 2020) Retrospective observational study among 34 patients found that treatment with hydroxychloroquine (n=21) was associated with longer time to negative viral PCR.(Mallat et al., 2020)
ACP June 16	Chloroquine is an immunomodulant drug. Prior studies on SARS-CoV demonstrated that it can block the SARS virus infection by reducing virus/cell fusion and endocytosis, along with host immunomodulation. It is primarily used to treat malaria but has also been shown effective in reducing viral replication of SARS-CoV and MERS-CoV. It does not have peer-reviewed clinical evidence for helpfulness in the treatment of Covid-19. Safety. QTc prolongation with torsadogenic potential is a known risk of each medication. Use in patients with a critical illness such as Covid-19, which is often accompanied by electrolyte abnormalities, raises additional concern. In a phase IIb clinical trial to assess safety and efficacy of two dose regimens of chloroquine (600mg twice daily for 10 days, or 450mg twice daily on 1 day then once daily for 4 days) combined with both ceftriaxone and azithromycin, 25% of the patients in the higher dose treatment arm presented with QTc>500ms. The study was halted prematurely due to safety concerns. . Effectiveness is likely limited, and any belief in its use is based on very weak and conflicting evidence. Early in vitro data and small nonrandomized reports suggested benefit; since then, higher quality and larger data sets have shown no significant benefit or have demonstrated worse outcomes: A prospective controlled clinical trial of hydroxychloroquine with 30 patients demonstrated no clinical benefit. A randomized parallel-group trial of 62 patients (non-peer-reviewed; flawed data set) showed shorter time to clinical recovery (without a measured mortality endpoint). 84 patients requiring oxygen who received hydroxychloroquine 600 mg daily did not differ from 97 similar but nonrandomized control patients in their rates of transfer to the ICU or all-cause death at 7 days. A non-peer-reviewed, preprint, retrospective analysis of 368 non-randomized, hospitalized patients with confirmed SARS-CoV-2 infection from all United States Veterans Health Administration medical centers found that hydroxychloroquine alone or with azithromycin was not associated with reduction of mechanical ventilation or mortality; an association with increased overall mortality was identified retrospectively in nonrandomized patients treated with hydroxychloroquine alone. An observational study of 1376 consecutive, non-randomized patients hospitalized for at least 24 hours with Covid-19 excluded those who were intubated during their first 24 hours. Those who received hydroxychloroquine did not have a significantly different risk of the composite end point of intubation or death, but they were also more severely ill at baseline with significantly lower Pao2:Fio2 than those who did not receive hydroxychloroquine. *CEP NOTE: The reviewers who are working with the ACP guideline developers intend to produce a living systematic review on this topic. Please see their published article for more information.*
EM-RAP June 18	Recent studies on hydroxychloroquine have found no benefit and possible risk of harm. Hydroxychloroquine should thus be avoided.
SIDP June 15	No evidence of clinical benefit of CQ/HCQ in hospitalized patients with COVID-19 We have seen harm: overdose and QTc prolongation which is additive with the cardiovascular toxicity seen with the COVID-19 infectious syndrome.
CADTH June 5	(June 5) Since the Addendum to the April 20, 2020 Brief Overview was published on May 29, 2020, The Lancet retracted an article that had significant impact on the conduct of clinical trials of hydroxychloroquine in the treatment of COVID-19. A review of the latest development and publication is ongoing and a report will be posted shortly. (May 29) Important new evidence became available since the original Brief Overview on the use of chloroquine or hydroxychloroquine, with or without azithromycin, for treating COVID-19 was posted on the CADTH website on April 20, 2020. This new information indicates that there is still uncertainty regarding the clinical benefit of using

Source	Findings
	these drug regimens for treating patients with COVID-19. It does, however, suggest that there may be potential harm associated with the use of chloroquine or hydroxychloroquine, with or without azithromycin. Some of the new studies have reported the occurrence of QTc prolongation on electrocardiographic readings; QTc prolongation may be associated with increased risk of severe cardiac arrythmia. Some research projects on hydroxychloroquine, including the WHO-sponsored Solidarity trial, have temporarily been halted in order to assess the safety data collected thus far on this drug.
Hopkins June 3	The overall feeling is that safety is an issue especially in more severely ill patients; however, it remains without high-quality data to argue for or against its use. Reported to have some efficacy in vitro and in limited, very low-quality evidence for COVID-19 pneumonia. The mechanism may be by interfering with cellular acidification in the phagolysosome. • Much hype and preliminary reports of efficacy are from press releases or small studies. • Growing safety signals that high dose or use in severely ill patients may contribute to cardiotoxicity. HCQ may cause prolonged QT, and caution should be used in critically ill COVID-19 patients who may have cardiac dysfunction or if combined with other drugs that cause QT prolongation. A combination with azithromycin may worsen QT interval problems.
CEBM May 30	The hypothesis that the 4-aminoquinolines chloroquine and hydroxychloroquine may be beneficial in the treatment of COVID-19 is a weak one, based on poor mechanistic reasoning and inconsistent results of studies in vitro, in laboratory animals, and in humans. It is likely that even if chloroquine and hydroxychloroquine are effective in COVID-19, the beneficial effects will be small. The risks of adverse reactions to these drugs may be increased in patients who are acutely ill with severe COVID-19, in many of whom high doses are being used. Macrolide antibacterial drugs, such as azithromycin, clarithromycin, erythromycin, and telithromycin, interact adversely with the 4-aminoquinolines, since both types of drug prolong the electrocardiographic QT interval. The combination increases the risk of the serious ventricular tachycardia called torsades de pointes, which is often fatal. Macrolide antibacterial drugs should be avoided in patients taking chloroquine or hydroxychloroquine. Other drugs that prolong the QT interval should also be avoided or used with care. *CEP NOTE: a June 4 addendum to this review notes the retraction of the published registry study claiming a higher mortality risk in patients treated with hydroxychloroquine or chloroquine.*

Medical center guidance on hydroxychloroquine for treatment of COVID-19

Hospital	Policy/recommendation
Mass. General June 24	Hydroxychloroquine should not be initiated outside of a clinical trial.
Brigham June 23	Hydroxychloroquine is not recommended outside of the context of a clinical trial. Upon review, the FDA concluded that it is unlikely that chloroquine or hydroxychloroquine may be effective in treating COVID-19 and that the benefits do not outweigh the risks for use in COVID-19, thereby revoking EUA 039 originally authorized on 3/28/20
Yale June 22	NOT currently recommended as first line treatment for COVID-19.
Penn Medicine June 20	Hydroxychloroquine is no longer recommended for use in hospitalized patients. For non-hospitalized patients, symptomatic treatment and supportive care are preferred, but patients are still being recruited for a clinical trial of hydroxychloroquine. Because hydroxychloroquine may inhibit antiviral activity of remdesivir, providers should consider stopping hydroxychloroquine in patients receiving remdesivir. However, the half-life of hydroxychloroquine is 20-40 days. The risks and benefits of stopping hydroxychloroquine should be weighed before stopping the medication, especially in patients on the medication chronically to treat inflammatory conditions.

Hospital	Policy/recommendation
UCSF June 5	Hydroxychloroquine should only be given in the context of a clinical trial.
Michigan June 3	The current body of literature and local experience does not support the routine use of any specific treatment regimen, including hydroxychloroquine, for patients with confirmed COVID-19 infection.

Key to sources referenced

ACP–American College of Physicians
ASHP–American Society of Health System Pharmacists
Australia– Australian National COVID-19 Clinical Evidence Taskforce (27 organizations represented)
CADTH–Canadian Agency for Drugs and Technologies in Health
CEBM–University of Oxford Centre for Evidence-based Medicine
EM-RAP–Emergency Medicine Reviews and Perspectives
FLARE–Massachusetts General Hospital Fast Literature Updates
NIH–National Institutes of Health COVID-19 Treatment Guidelines Panel
Living Evidence–an ad hoc collaboration of Cochrane Collaboration members and hospital health technology assessment specialists
SIDP–Society of Infectious Disease Pharmacists

Other guideline issuers whose recommendations are outdated (issued prior to May 15)

American Thoracic Society
Canadian multi-specialty task force
Surviving Sepsis Campaign

Update history (key additions and changes)

June 27: Updated guidelines, evidence reviews, and hospital guidance. New section added for systematic reviews. Guidance more than one month old removed. Summary conclusions updated.

May 18: Updated NIH and hospital guidance and evidence reviews, new evidence review from ACP. Guidance more than one month old has been removed from the tables. Hospital evidence reviews incorporated into evidence review table. No changes to summary conclusions.

April 30: New guidance from NIH, updated guidance from FDA and CPA. New evidence reviews from MGH (FLARE), NIH and CADTH, updated reviews from CEBM and SIDP. Guidance more than one month old has been removed from the tables. Updated hospital guidance. New conclusions regarding guidance discouraging use outside clinical trials because of uncertain benefits and risk of adverse events.

April 22: More detailed hospital guidance: some hospitals now testing HCQ in outpatient clinical trials, evidence review table streamlined.

April 14: 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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