COVID-19: TREATMENT WITH HYDROXYCHLOROQUINE (HCQ)

A Rapid Guidance Summary from the Penn Medicine Center for Evidence-based Practice
Last updated May 1, 2020 4:00 pm All links rechecked April 30 unless otherwise noted.

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

- Use of hydroxychloroquine and chloroquine for treatment of COVID-19 disease is considered an off-label indication. Clinical trials are in progress.
- Current clinical evidence on hydroxychloroquine is from small, low-quality studies, with results (GRADE strength of evidence evaluation: very low).
- The most recent guidance discourages use of hydroxychloroquine outside of clinical trials.
- The most recent evidence reviews have stressed the weakness of clinical trials reported to date and the increasing recognition of adverse events from hydroxychloroquine.
- None of the hospitals recommend use of hydroxychloroquine for treatment of outpatients outside of clinical trials.

Guidelines on hydroxychloroquine for treatment of COVID-19 disease

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendations</th>
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<tr>
<td><strong>Public health agencies</strong></td>
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<tr>
<td>CDC April 25</td>
<td>There are no drugs or other therapeutics presently approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19. Current clinical management includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated.</td>
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<tr>
<td>FDA April 24</td>
<td>There are currently no FDA-approved medical countermeasures for COVID-19. Because chloroquine phosphate and hydroxychloroquine may possibly help very sick patients, FDA is allowing these drugs to be provided to certain hospitalized patients under an Emergency Use Authorization issued March 28. Under the EUA, health care providers and patients are provided with information about the risks of these drugs. However, more data from clinical trials are necessary for us to determine whether chloroquine phosphate or hydroxychloroquine sulfate are safe and effective in treating or preventing COVID-19. 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. If a healthcare professional is considering use of hydroxychloroquine or chloroquine to treat or prevent COVID-19, FDA recommends checking <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> for a suitable clinical trial and consider enrolling the patient. Consider using resources available to assess a patient’s risk of QT prolongation and mortality. Emergency Use Authorization is only applicable to hospitalized patients.</td>
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<td>Ontario April 24</td>
<td>Chloroquine or hydroxychloroquine is not recommended outside of approved clinical trials or where other indications would justify its use.</td>
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<td>NIH April 21</td>
<td>There are insufficient clinical data to recommend either for or against using chloroquine or hydroxychloroquine for the treatment of COVID-19 (strong recommendation, based on expert opinion). When chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects (AEs), especially prolonged QTc interval (strong recommendation, based on expert opinion). The Panel recommends against the use of hydroxychloroquine plus azithromycin for the treatment of COVID-19, except in the context of a clinical trial (strong recommendation, based on expert opinion).</td>
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**Source** | **Recommendations**
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INESS April 4 | No data support recommending the use of chloroquine or hydroxychloroquine outside of a research protocol in patients with a confirmed diagnosis of COVID-19 whose clinical condition does not require hospitalization. The uncertain nature of the data documenting the efficacy of these drugs does not support recommending the use of chloroquine or hydroxychloroquine, with or without azithromycin, outside of a research protocol in patients with a confirmed diagnosis of COVID-19 whose clinical condition requires hospitalization. The use of chloroquine or hydroxychloroquine in patients with a confirmed diagnosis of COVID-19 who are admitted to intensive care is not recommended outside of a research protocol.

**Professional societies**

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<td>CPA April 17</td>
<td>Data to date are preliminary; no significant effect on disease morbidity or mortality has been demonstrated. Use of chloroquine or hydroxychloroquine in COVID-19 patients may be associated with significant adverse effects. Use of chloroquine or hydroxychloroquine for COVID-19 should be restricted to hospitalized patients until more data are available.</td>
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<td>IDSA April 11</td>
<td>Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap)</td>
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<td>AAFP April 7</td>
<td>While there have been limited studies performed, with varying degrees of success, the data do not support improved patient-oriented outcomes with these medications. Until further testing is completed, the AAFP cautions against prescribing these medications outside of their current indicated uses.</td>
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| ATS April 3 | For patients who are well enough to be managed as outpatients, we make no suggestion either for or against hydroxychloroquine (or chloroquine). 18% for intervention, 36% no suggestion, and 46% against.

For hospitalized patients with COVID-19 who have no evidence of pneumonia, we make no suggestion either for or against hydroxychloroquine (or chloroquine). 8% for intervention, 50% no suggestion, and 42% against.

For hospitalized patients with COVID-19 who have evidence of pneumonia, we suggest hydroxychloroquine (or chloroquine) on a case-by-case basis. Requirements include all of the following: a) shared decision-making in which the patient is informed about the possible benefits and potential side effects, b) collection of data in a manner that enables studies that use valid methods for causal inference and control of confounders for the purpose of interim assessment, c) the patient's clinical condition is sufficiently severe to warrant investigational therapy, and d) there is not a shortage of drug supply. 73% for intervention, 16% no suggestion, and 11% against. |

**Evidence reviews on hydroxychloroquine for treatment of COVID-19 disease**

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<td>MGH (FLARE) April 29</td>
<td>Initial enthusiasm for chloroquine and hydroxychloroquine for treatment of SARS-CoV-2 infection spurred a number of clinical trials, some with newly published data. Though the majority of available clinical data have not been peer reviewed, no studies demonstrate significant differences in relevant clinical outcomes. Furthermore, enthusiasm for these medications has waned amidst worrisome safety signals in patients receiving hydroxychloroquine and azithromycin. We eagerly await the peer-reviewed published data from these hydroxychloroquine trials (and from the publicized, but not yet released, remdesivir NIAID trial), to further refine the armamentarium for COVID-19.</td>
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<td>ASHP</td>
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<td>Hopkins</td>
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<td>NIH</td>
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<td>CADTH</td>
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Still no clear evidence of clinical benefit with either HCQ or CQ, especially in critically ill patients. We have seen harm: overdose and QTc prolongation: we should be monitoring ECG and considering withholding for QTc > 450 (men) or >470 (women). PK/PD based dosing regimens are limited by PK assumptions (Kp), and an unknown PD target (i.e. immune-modulation vs. direct antiviral activity).

Current data do not support the use of hydroxychloroquine for prophylaxis or treatment of COVID-19. There are no published trials of prophylaxis. Two trials of hydroxychloroquine treatment that are in the public domain, one non-peer reviewed, are premature analyses of trials whose conduct in both cases diverged from the published skeleton protocols registered on clinical trial sites. Neither they, nor three other negative trials that have since appeared, support the view that hydroxychloroquine is effective in the management of even mild COVID-19 disease.

We currently know of 142 registered clinical trials involving the use of chloroquine or hydroxychloroquine or both in some capacity, either as interventions being tested or as comparators for other drugs. Only 35% of those are designed to be blinded. We await the results of those studies.

The currently available best evidence failed to demonstrate or to exclude a beneficial effect of HCQ on clinical progression of COVID-19 (as inferred by radiological findings; risk ratio: 0.61; 95% CI: 0.26, 1.43), or on viral clearance by PCR tests (RR: 2.00; 95% CI: 0.02, 20.00), although a somewhat higher proportion in the HCQ group experienced clinical improvement (RR: 1.47; 95% CI 1.02, 2.11). However, the certainty in the evidence was rated as very low mainly due to small sample sizes (sparse data), co-interventions, and risk of bias due to methodological limitations. In addition, the selected outcomes should be considered indirect, as important patient outcomes (e.g., mortality, rate of progression to ARDS and need for mechanical ventilation) were unavailable. GRADE evaluation of evidence for all outcomes: very low.

**Medical center guidance on hydroxychloroquine for treatment of COVID-19**

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<td>Brigham April 28</td>
<td>Hydroxychloroquine is not routinely recommended, unless as part of a clinical trial. Outside of a clinical trial, hydroxychloroquine may be considered for patients who are hospitalized with COVID-19, only after weighing the risks and benefits.</td>
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| Penn Medicine April 23 | **Hospitalized patients (including critically ill):** There are no data to support routine use of hydroxychloroquine to treat these patients, and there are safety concerns from available data on chloroquine and hydroxychloroquine so use is recommended only in setting of clinical trial.  
**Non-hospitalized patients:** Based on available data on chloroquine and hydroxychloroquine risk of hydroxychloroquine outweighs any theoretical benefit for non-hospitalized patients outside of a clinical trial. There are significant safety concerns in patients that cannot be closely monitored.  
Emerging data on the use of chloroquine and hydroxychloroquine calls into question the efficacy and safety of these agents for the treatment of SARS-CoV-2. |
| Washington April 22 | **Inpatients with lower respiratory tract infection and oxygen requirement or mechanical ventilation:** Hydroxychloroquine is no longer recommended. Recommend clinical trial. If HCQ is started outside of a clinical trial, obtain baseline EKG and share decision-making with the patient. Note: Starting HCQ may disqualify from clinical trial enrollment.  
**Outpatients:** Hydroxychloroquine is not recommended. Consider clinical trial enrollment.  
Recent clinical studies have not demonstrated virologic or clinical benefits, see evidence summary for details. |
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| **Mass. General April 20** | **For hospitalized patients with moderate or severe disease** (vital signs or lab results indicative of risk of progression): A randomized clinical trial is now open at MGH, comparing hydroxychloroquine (HCQ) versus placebo. 400 mg PO BID x2 followed by 400 mg daily while hospitalized, up to 5 days. Chloroquine has activity but limited supply so hydroxychloroquine preferred.  
**For hospitalized patients whose disease is mild**: Supportive care recommended, hydroxychloroquine or chloroquine not indicated in these patients. |
| Nebraska April 17 | Efficacy unproven and toxicity risk noteworthy; closely monitor for safety. ID consultation required. An in vitro inhibitor of SARS-CoV-2, but with multiple inconclusive, uncontrolled, or non-peer-reviewed early clinical reports. The bulk of clinical reports have now relayed negative results; one research group is responsible for most of the positive clinical reports. Being investigated for all stages of disease severity; use for prophylaxis appropriate only within a registered clinical trial. Use with caution in pediatrics. Impact of immunosuppressive effects is unknown. Has been studied in combination with azithromycin, without additive benefit but potential for additive cardiac toxicities (see below). Use for COVID-19 may exacerbate current shortages for patients with well-accepted autoimmune indications. |
| **Michigan April 15** | **Inpatient**: The current body of literature and local experience does not support the routine use of hydroxychloroquine for patients with confirmed COVID-19 infection. Michigan Medicine is committed to participation in randomized controlled clinical trials to facilitate the generation of robust evidence concerning the effectiveness of products in treating COVID-19 and to appropriately delineate risk-vs-benefit assessments for various treatment strategies.  
**Outpatient**: The data is not strong enough to recommend routine use of hydroxychloroquine. |
| **Yale April 14** | **Inpatients with severe disease** (respiratory failure): Start hydroxychloroquine (400mg PO q12h x 24h followed by 200mg q12h x 4 days for a 5 day total duration then re-assess); Consider tocilizumab x 1 dose (in combination with hydroxychloroquine).  
**Inpatients with non-severe disease**: Start treatment with hydroxychloroquine (as above) if the patient has oxygen saturation < 93% on room air, or is on chronic oxygen supplementation or has clinical disease (fever / symptoms / lung opacities on chest x-ray) AND risk factors for progression (Age ≥ 60, BMI ≥ 30, diabetes, chronic heart disease, hypertension, chronic lung disease, or is immunosuppressed).  
Outpatient prescribing of hydroxychloroquine, HIV-1 protease inhibitors, and azithromycin should be reserved ONLY for patients who have medical conditions where their use has been established and there are no other alternatives. |
| **UCSF April 6** | Most patients with confirmed upper respiratory tract infection from COVID-19 should not be offered experimental medications.  
**Lower respiratory tract infections**: Outside of the context of clinical trial, providers considering hydroxychloroquine as part of COVID-19 treatment should weigh the risks and benefits for the individual, evaluate for comorbidities and drug interactions that may affect safety of HCQ administration, and monitor during treatment. Consider hydroxychloroquine for patients with COVID-19 meeting requiring any of the following interventions: mechanical ventilation, non-invasive ventilation, or supplemental oxygen via high-flow nasal cannula. |
| **Toronto April 6** | Chloroquine and hydroxychloroquine (with or without azithromycin) is not recommended for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use (e.g. chronic rheumatological conditions). |

**Key to sources referenced**
INESS- Institut national d'excellence en santé et services sociaux (Quebec)  
IDSA–Infectious Disease Society of America  
AAFP–American Academy of Family Physicians  
ATS–American Thoracic Society  
CPA–Canadian Pharmacists Association  
ASHP–American Society of Health System Pharmacists  
SIDP–Society of Infectious Disease Pharmacists
Update history (key additions and changes)

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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Appendix. Studies in ASHP evidence table as of May 1, 2020 (click here for study added since previous edition of this report)

Hydroxychloroquine small pilot study conducted in China: 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV. Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up).

Hydroxychloroquine randomized, parallel group study in adults in China (ChiCTR2000029559): 31 pts with COVID19 and pneumonia received hydroxychloroquine sulfate (200 mg twice daily for 5 days) and standard treatment (O2, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids) and 31 other pts received standard treatment alone (control group). Exclusion criteria included severe and critical illness. Pts assessed at baseline and 5 days after treatment initiation for time to clinical recovery (TTCC; defined as normalization of fever and cough relief maintained for >72 hours), clinical characteristics, and changes on chest CT. It was concluded that hydroxychloroquine was associated with symptom relief since time to fever normalization was shorter in hydroxychloroquine group (2.2 days) vs control group (3.2 days), time to cough remission was shorter in hydroxychloroquine group, and pneumonia improved in 25/31 pts (80.6%) in hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group).

Note: This study did not include pts with severe disease and pts received other anti-infectives in addition to hydroxychloroquine. At study entry, 9 pts without fever and 9 pts without cough were included in hydroxychloroquine group and 14 pts without fever and 16 pts without cough were included in control group; unclear how these pts were addressed in TTCC calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and a placebo group (each with 100 pts) and primary end points of time to negative nucleic acid and T-cell recovery, data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported.
Hydroxychloroquine with azithromycin open-label, nonrandomized study in France: Preliminary data from an ongoing study in hospitalized pts with confirmed COVID-19 was used to assess efficacy of hydroxychloroquine used alone or with azithromycin; untreated pts were used as a negative control. The primary end point was negative PCR results in nasopharyngeal samples at day 6. Data from 14 pts treated with hydroxychloroquine (200 mg 3 times daily for 10 days), 6 pts treated with hydroxychloroquine and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5), and 16 pts in the control group were analyzed. At day 6, 8/14 (57%) in the hydroxychloroquine group, 6/6 (100%) in the hydroxychloroquine and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results. At day 8, a positive PCR was reported in a pt treated with both drugs who had tested negative at day 6. Note: This was a small nonrandomized study that didn't appear to be designed to compare hydroxychloroquine vs hydroxychloroquine and azithromycin (pts received antibiotics to prevent bacterial superinfection based on clinical judgment). Data on disease severity was unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented.

Hydroxychloroquine with azithromycin open-label, uncontrolled study in France: 11 adults hospitalized with COVID-19 received hydroxychloroquine (600 mg daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). At time of treatment initiation, 8/11 pts had significant comorbidities associated with poor outcomes and 10/11 had fever and received O2. Within 5 days, 1 pt died and 2 transferred to ICU; the regimen discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested. Note: In this small uncontrolled study, hydroxychloroquine and azithromycin regimen did not result in rapid viral clearance or provide clinical benefit.

Hydroxychloroquine with azithromycin uncontrolled, observational study in France: 80 adults with confirmed COVID19 were treated with hydroxychloroquine (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O2 saturation, temperature, BP, pulse, level of consciousness); only 15% had fever; 4 pts were asymptomatic carriers; mean time from onset of symptoms to treatment initiation was 4.9 days. Clinical outcome, contagiousness as assessed by nasopharyngeal PCR assay and culture, and length of stay in infectious disease (ID) unit were evaluated in pts who were treated for at least 3 days and followed for at least 6 days. Favorable outcome was reported for 81.3%; 15% required O2; 3 pts transferred to ICU; 1 pt died; mean time to discharge from ID unit was 4.1 days. At day 8, PCR results were negative in 93% of those tested; at day 5, viral cultures were negative in 97.5% of those tested. Note: Almost all pts were considered low risk for clinical deterioration (including 4 pts described as asymptomatic carriers) and it is unclear how many would have had spontaneous conversion to negative nasopharyngeal samples during same time frame. Although 80 pts were enrolled, PCR results available for fewer pts beginning on day 3 and only 60 pts represented in day 6 data. This was an uncontrolled study and data presented cannot be used to determine whether a regimen of hydroxychloroquine with azithromycin provides benefits in terms of disease progression or decreased infectiousness, especially for pts with more severe disease.

[NEW STUDY ADDED April 29] Hydroxychloroquine (with or without azithromycin) in a retrospective analysis of patients hospitalized with COVID-19 in US Veterans Health Administration medical centers: Data for 368 males (median age >65 years) treated with hydroxychloroquine in addition to standard supportive management were analyzed for death rate and need for mechanical ventilation. Death rate was 27.8% (27/97) in those treated with hydroxychloroquine, 22.1% (25/113) in those treated with hydroxychloroquine and azithromycin, and 11.4% (18/158) in those not treated with hydroxychloroquine; rate of ventilation was 13.3, 6.9, and 14.1%, respectively. Use of hydroxychloroquine alone (but not use of hydroxychloroquine and azithromycin) was associated with increased overall mortality compared with no hydroxychloroquine; use of hydroxychloroquine with or without azithromycin did not reduce the risk of mechanical ventilation. Note: The pt population included only elderly males 59-75 years of age, many with significant comorbidities. This analysis did not look at efficacy measures.

Efficacy measures: Initial studies evaluating hydroxychloroquine based efficacy of the drug on negative conversion in nasopharyngeal samples at day 6 or 7. RTPCR tests using upper and lower respiratory specimens (including nasopharyngeal and oropharyngeal swabs) are recommended for diagnosis of COVID-19; however, dynamics of SARS-Cov-2 in infected patients (untreated or treated) and presence of the virus at various body sites over the course of infection have not been fully determined.