New York State Medicaid
Drug Information Response Center

NEW YORK STATE Department of Health | Office of Health Insurance Programs

SUNY The State University of New York

What are the data regarding use of hydroxychloroquine sulfate (Plaquenil®) in combination with azithromycin (Zithromax®/Z-Pak®) for the treatment of COVID-19?

Initial response: March 25, 2020
Update 5: July 7, 2020

Summary of changes:

- Governmental and professional organizations have updated their guidance regarding the use of chloroquine (CQ) and hydroxychloroquine sulfate (HCQ) with or without azithromycin (AZ) to treat COVID-19.[1-5] Most notably, the Food and Drug Administration has revoked the Emergency Use Authorization of CQ and HCQ.[2]
- Two recently published randomized controlled trials, 1 evaluating the use of HCQ for prevention[6] and 1 for treatment of COVID-19,[7] showed no benefit and increased side effects with HCQ compared to placebo or standard of care, respectively.

Publication	Date	HCQ-related recommendations
Governmental		
NIH Guidelines[1]	Jun 16	• The panel recommends against CQ or HCQ for treatment of COVID-19 except within a clinical trial. • The panel recommends against HCQ+AZ, except within a clinical trial, due to potential for toxicities.
FDA warning[2]	Jun 15	• Coadministration of CQ or HCQ with remdesivir is not recommended, due to *in vitro* data demonstrating reduced antiviral activity of remdesivir in the presence of CQ or HCQ.
FDA revokes EUA[3]	Jun 15	• The EUA for CQ and HCQ to treat COVID-19 was revoked based on accumulation of data indicating they may not be effective and the potential benefits do not outweigh the known and potential risks.
EMA Public Health Statement[4]	May 29	• A reminder was issued to closely monitor patients with COVID-19 receiving CQ or HCQ due to risk of serious adverse effects, including cardiovascular and neuropsychiatric events. • Beneficial effects of CQ and HCQ have not been established in patients with COVID-19. • CQ and HCQ should only be used in the context of clinical trials for prevention or treatment of COVID-19 or in national emergency use programs.
Professional		
IDSA Guidelines[5]	Jun 18	• Due to uncertainty regarding risks and benefits, the panel continues to recommend that HCQ only be used to treat patients with COVID-19 in the context of a clinical trial. Due to potential for toxicity, the panel recommends against the use of HCQ+AZ outside a clinical trial.

AZ=azithromycin; CQ=chloroquine; EMA=European Medicines Agency; EUA=emergency use authorization; FDA=Food and Drug Administration; HCQ=hydroxychloroquine; IDSA=Infectious Diseases Society of America; NIH=National Institutes of Health.

Study	Objective/Design	Population	Intervention/Endpoint	Results*
Boulware et al[6] NEJM June 3	To test effectiveness of HCQ as postexposure prophylaxis DB, PC, RCT	Adults in the United States & Canada with household or occupational exposure to someone with confirmed COVID-19	Placebo or HCQ 800 mg, followed by 600 mg in 6-8 hours, then 600 mg daily x 4 days Incidence of lab-confirmed or illness consistent with COVID-19 within 14 days	• 719/821 (87.6%) reported high-risk exposure • Incidence of new illness did not differ between groups: ○ HCQ: 49/114 (11.8%) ○ Placebo: 58/407 (14.3%) ○ Absolute difference −2.4% [−7.0 to 2.2], p=0.35 • Side effects were more common with HCQ vs. placebo (40.1% vs. 16.8%; p<0.001).
Tang et al[7] BMJ Open Access May 14	To assess efficacy and safety of HCQ + SOC vs. SOC alone in adults with COVID-19 MC, OL, RCT	Hospitalized adults in China with lab-confirmed COVID-19	HCQ loading dose 1200 mg daily x 3 days, followed by 800 mg daily x 2 or 3 weeks (in mild-moderate or severe disease, respectively) Primary endpoint: negative conversion of SARS-CoV-2 by 28 days**	• 148/150 (93.3%) had mild-moderate disease • 109 (73%) had negative conversion before 28 days; no significant difference between groups: ○ HCQ+SOC: 85.4% [73.8 to 93.8] ○ SOC: 81.3% [71.2 to 89.6] ○ Difference: 4.1% [–10.3 to 18.5] • Median time to conversion was similar: ○ HCQ+SOC: 8 days [5 to 10] ○ SOC: 7 days [5 to 8] ○ HR: 0.85 [0.58 to 1.23], p=0.34 • Adverse events were more common with HCQ+SOC vs. SOC alone (30% vs. 9%; no p-value).

*95% confidence interval reported in brackets.
**A second primary endpoint of clinical improvement by 28 days was not analyzed because the trial was stopped early and insufficient numbers of patients with severe disease were enrolled.
DB=double blind; HCQ=hydroxychloroquine; HR=hazard ratio; MC=multi-center; OL=open label; PC=placebo-controlled; RCT=randomized controlled trial; SOC=standard of care

References: 1. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/. 2. Food and Drug Administration. https://www.fda.gov/safety/medical-product-safety-information/remdesivir-gilead-sciences-fda-warns-newly-discovered-potential-drug-interaction-may-reduce. 3. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and. 4. European Medicines Agency. https://www.ema.europa.eu/en/news/covid-19-reminder-risks-chloroquine-hydroxychloroquine. 5. Infectious Diseases Society of America. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
6. Boulware et al. *NEJM* 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa2016638. 7. Tang et al. *BMJ* 2020. https://www.bmj.com/content/369/bmj.m1849.