Avoidance of hydroxychloroquine in outpatient settings – Evidence Document

- Current recommendations:
    - NIH: **Recommends against** use of hydroxychloroquine (HCQ) or chloroquine for treatment of COVID-19, particularly outside of a hospital, except in clinical trial
        - **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 trials
    - IDSA: **Suggests against** HCQ plus azithromycin outside of clinical trials
    - FDA: **Cautions against use** of HCQ for COVID-19 outside of hospital or clinical trial due to risk of arrhythmias
        - 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 benefit
    - 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 events
- Adverse events:
    - QTc prolongation, ventricular arrhythmia, cardiac death, drug-drug interactions, hypoglycemia
- Select Evidence:
    - Treatment for outpatients with mild/moderate COVID-19
        - Skipper CP et al. Ann Inter Med, July 16, 2020 – Among 423 outpatients **no significant decrease in primary outcome of change in symptom score** (0-10 scale) over a 14-day period (-2.60 with HCQ v -2.33 with placebo, P=0.117) was observed. No significant difference in symptom resolution, incidence of hospitalization, or death, with 1 death occurring in each group. Higher rate of adverse events with HCQ (43%) compared to placebo (22%).
        - Mitja O et al. CID, July 16, 2020 – Among 293 **patients no significant difference found in mean reduction of viral load at day 3 or day 7 nor reduced risk of hospitalization** (5.9% with HCQ v 7.1% with no antiviral treatment). Time to resolution of symptoms was also not reduced with HCQ (10 days) compared to no antiviral treatment (12 days).
    - Treatment for hospitalized patients with mild/moderate COVID-19
        - Cavalcanti AB et al. NEJM, July 23, 2020 – Among 504 patients (40% requiring supplemental oxygen prior to enrollment) comparing standard of care alone (SOC), HCQ plus azithromycin with SOC, or HCQ with SOC, there was **no observed benefit** with HCQ nor HCQ + azithromycin at day 15. Primary outcome of clinical status improvement measured by 7-point ordinal scale demonstrated that odds of having a higher score (worse outcome) was 1.21 (CI 0.69-2.11) with HCQ alone, 0.99 (CI 0.57-1.73) with HCQ plus azithromycin compared to SOC. Adverse events including QTc prolongation (14.7% with HCQ v 1.7% with SOC) and liver enzyme elevations (10.9% with HCQ v 3.4% with SOC) were more frequent in patients receiving HCQ or HCQ + azithromycin compared to SOC.
        - Tang W et al. BMJ, May 6, 2020 – Among 150 patients, HCQ with SOC compared to SOC alone **did not significantly improve rate of negative conversion of virus** at 30 days (85.4%

with HCQ v 81.3% with SOC). Increased rate of adverse events reported in patients receiving HCQ (30%) compared to SOC (9%).

- Treatment for hospitalized patients with severe COVID-19
  - Horby et al. medrxiv RECOVERY trial, July 15, 2020 – Among 4716 randomized to receive HCQ or usual care alone, **no difference in mortality** was observed in patients receiving HCQ (26.8%) or usual care (25.0%) regardless of oxygenation requirement (room air, supplemental oxygen, or mechanically ventilated). Those receiving HCQ were less likely to be discharge from the hospital alive (60.3% with HCQ v 62.8% with usual care) and more likely to advance to requiring invasive mechanical ventilation or death (29.8% with HCQ v 26.5% with usual care).
  - Arshad S et al. IJFD, July 1, 2020 (Observational, non-randomized) – Among 2541 patients HCQ plus azithromycin and HCQ alone reduced mortality compared to neither treatment (20.1% with HCQ + azithromycin, 13.5% with HCQ alone, 26.4% with neither). Among patients **receiving HCQ alone or HCQ plus azithromycin, 78.9% and 74.3% of patients also received concurrent corticosteroids compared to only 35.7% of patients who received neither drug**. As demonstrated in the RECOVERY randomized, controlled trial, dexamethasone confers mortality benefit in severe COVID-19. Additionally, 20% of included patients deemed as controls did not receive HCQ likely due to death prior to receipt of HCQ, determination by clinicians not to treat aggressively due to poor prognosis (sought comfort care), or were treated prior to widespread implementation of HCQ use in treatment protocol. This is supported by the rapidly observed difference in mortality by day 2 (8% difference between HCQ and no treatment, which would not be routinely observed in randomized trials) along with the fact that **control patients were twice as likely to die yet half as likely to receive ICU-level care (20.2% with HCQ alone, 37.0% with HCQ + azithro, 15.2% with neither drug) or mechanical ventilation (13.8% with HCQ alone, 29.9% with HCQ + azithro, 8.3% with neither drug).**
- Post-exposure prophylaxis
  - Boulware D et al. NEJM, June 3, 2020 – **No impact observed for development of confirmed or probable COVID-19** (11.8% with HCQ v 14.3% with placebo, P=0.35) among 821 patients
  - Mitja O et al. Preprint medrxiv, July 26, 2020 – Among 2314 patients **no difference observed in development of PCR confirmed and symptomatic COVID-19** (6.2% with HCQ v 5.7% with no therapy), confirmed or symptomatic COVID-19 (17.8% with HCQ v 18.7% with no therapy). Higher rate of adverse events occurred in patients receiving HCQ (51.6%) compared to no therapy (5.9%).

- Conclusion: **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 and concern for potential adverse events.**

Author	Journal	Population	Intervention	Control	Balanced?	Outcome	Adverse Events
Raoult	Travel Medicine and Infectious Disease	Mostly outpatient	HCQ x 10 days + Az for 5 days	Other treatments	No	0.5% vs. 3.1% death rate, p=0.0002	4.3% vs 0.6%
Tang	BMJ	Hospitalized	HCQ x 3 weeks	Usual Care	Yes (RCT)	85.4% vs 81.3% viral clearance, p=0.34	30% vs. 9%.
Boulware	NEJM	High-risk exposure	HCQ x 5 days	Placebo	Yes (RCT)	11.8% vs 14.3% infection rate, p=0.35	40% vs. 17%
Skipper	Annals of IM	Outpatient, early disease	HCQ x 5 days	Placebo	Yes (RCT)	2.6 vs. 2.3 points improvement in symptoms P=0.12	43% vs. 22%
Mitja	Clin Inf. Disease	Outpatient, early disease	HCQ x 7 days	Usual care	Yes (RCT)	3.44 log reduction vs. 3.37 log reduction	72% vs. 8.7%
Cavalcanti	NEJM	Hospitalized	HCQ OR HCQ + AZ x 7 days.	Usual Care	Yes (RCT)	Median score 1 vs 1 vs 1	33.7% vs 39.3% vs 22.6%
RECOVERY Trialists	Medrxiv (PREPRINT!)	Hospitalized	HCQ x 10 days	Placebo	Yes (RCT)	26.8% vs. 25% 28-day mortality, p=0.18	Not reported

Source: Wilson P. Hydroxychloroquine for COVID-19: What's the Evidence?. Medscape. https://www.medscape.com/viewarticle/927342. Published 2020. Accessed August 6, 2020.

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