

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 4: May 19, 2020

Summary of changes:

- Results of 2 large observational studies evaluating the use of hydroxychloroquine (HCQ) alone or in combination with azithromycin (AZ) for treatment of hospitalized patients with COVID-19 in New York City were published.
 - Rosenberg et al, published online **May 11, 2020**, found no significant difference in in-hospital mortality among patients treated with HCQ + AZ, HCQ alone, or AZ alone compared to receiving neither drug; cardiac arrest was more likely in patients who received HCQ + AZ compared to neither drug.¹
 - Geleris et al, published online **May 7, 2020**, found that use of HCQ was not associated with either a decreased or increased risk of intubation or death and results were similar with use of AZ.²

Published Literature:

Study	Objective/Design	Population	Exposures/Endpoints	Results
Rosenberg et al ¹ JAMA May 11	To describe clinical outcomes associated with use of HCQ ± AZ in hospitalized patients with COVID-19 Retrospective, multicenter cohort from a random sample	Patients admitted with lab-confirmed COVID-19 to 25 hospitals in New York City	1. HCQ + AZ 2. HCQ alone 3. AZ alone 4. Neither drug Dosing of drugs was variable; duration not reported. <u>Primary endpoint:</u> in-hospital mortality <u>Secondary endpoints:</u> cardiac arrest and abnormal ECG (arrhythmia or QT prolongation)	Total of 1438 patients; 59.7% male; median age, 63 years. <u>Overall in-hospital mortality (95% CI):</u> 20.3% (18.2%-22.4%) <u>Probability of death (95% CI):</u> HCQ + AZ (n=735): 25.7% (22.3%-28.9%) HCQ alone (n=271): 19.9% (15.2%-24.7%) AZ alone (n=211): 10.0% (5.9%-14.0%) Neither drug (n=221): 12.7% (8.3%-17.1%) <u>Adjusted HR (95% CI) compared to neither drug:</u> HCQ + AZ: 1.35 (0.76-2.40) HCQ alone: 1.08 (0.63-1.85) AZ alone: 0.56 (0.26-1.21) <u>Adjusted OR (95% CI) for likelihood of cardiac arrest compared to neither drug:</u> HCQ + AZ: 2.3 (1.12-4.05) HCQ alone: 1.91 (0.96-3.81) AZ alone: 0.64 (0.27-1.56) No significant differences between any treatments in likelihood of abnormal ECG.
Geleris et al ² NEJM May 7	To examine the association between HCQ use and intubation or death in hospitalized patients with COVID-19 Retrospective cohort	Consecutive patients admitted with lab-confirmed COVID-19 to a large medical center in New York City	HCQ vs. No HCQ HCQ ± AZ was a suggested option for moderate-severe disease, per hospital guidance: HCQ 600 mg twice on day 1, then 400 mg daily x 4 days; AZ 500 mg on day 1, then 250 mg daily x 4 days. <u>Primary endpoint:</u> time from study baseline (24 hours after arrival at emergency department) to intubation or death (composite)	Total of 1446 consecutive patients; 1376 were included in the analysis; 811 (58.9%) received HCQ (median duration 5 days); 486/811 patients (59.9%) who received HCQ also received AZ. Over a median follow-up of 22.5 days, 346 patients (25.1%) were intubated or died. Use of HCQ was not significantly associated with the composite endpoint of time to intubation or death from baseline based on multivariable analysis with inverse probability weighting according to propensity score: HR 1.04 (95% CI, 0.82-1.32). Use of AZ was also not significantly associated with the composite endpoint of time to intubation or death from baseline: HR 1.03 (95% CI, 0.81-1.31).

AZ=azithromycin; CI=confidence interval; ECG=electrocardiogram; HCQ=hydroxychloroquine; HR=hazard ratio; JAMA=Journal of the American Medical Association; NEJM=New England Journal of Medicine; OR=odds ratio