



COVID-19 Treatment Guidelines

Chloroquine or Hydroxychloroquine and/or Azithromycin

Drug Info

Last Updated: July 8, 2021

Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, in addition to malaria.

Both chloroquine and hydroxychloroquine increase the endosomal pH, which inhibits fusion between SARS-CoV-2 and the host cell membrane.¹ Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 (ACE2) receptor, which may interfere with the binding of SARS-CoV to the cell receptor.² In vitro studies have suggested that both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, possibly preventing the release of the viral genome.³ Both chloroquine and hydroxychloroquine also have immunomodulatory effects, which have been hypothesized to be another potential mechanism of action for the treatment of COVID-19. Azithromycin has antiviral and anti-inflammatory properties. When used in combination with hydroxychloroquine, it has been shown to have a synergistic effect on SARS-CoV-2 in vitro and in molecular modeling studies.^{4,5} However, despite demonstrating antiviral activity in some in vitro systems, neither hydroxychloroquine plus azithromycin nor hydroxychloroquine alone reduced upper or lower respiratory tract viral loads or demonstrated clinical efficacy in a rhesus macaque model.⁶

The safety and efficacy of chloroquine or hydroxychloroquine with or without azithromycin and azithromycin alone have been evaluated in randomized clinical trials, observational studies, and/or single-arm studies. Please see [Table 2b](#) for more information.

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **chloroquine or hydroxychloroquine** and/or **azithromycin** for the treatment of COVID-19 in hospitalized patients (**AI**) and in nonhospitalized patients (**AIIa**).

Rationale

Hospitalized Patients

In a large randomized controlled platform trial of hospitalized patients in the United Kingdom (RECOVERY), hydroxychloroquine did not decrease 28-day mortality when compared to the usual standard of care. Patients who were randomized to receive hydroxychloroquine had a longer median hospital stay than those who received the standard of care. In addition, among patients who were not on invasive mechanical

ventilation at the time of randomization, those who received hydroxychloroquine were more likely to subsequently require intubation or die during hospitalization than those who received the standard of care.⁷

The results from several additional large randomized controlled trials have been published; these trials have failed to show a benefit for hydroxychloroquine with or without azithromycin or azithromycin alone in hospitalized adults with COVID-19. In the Solidarity trial, an international randomized controlled platform trial that enrolled hospitalized patients with COVID-19, the hydroxychloroquine arm was halted for futility. There was no difference in in-hospital mortality between patients in the hydroxychloroquine arm and those in the control arm.⁸ Similarly, PETAL, a randomized, placebo-controlled, blinded study, was stopped early for futility. In this study, there was no difference in the median scores on the COVID Outcomes Scale between patients who received hydroxychloroquine and those who received placebo.⁹ Data from two additional randomized studies of hospitalized patients with COVID-19 did not support using hydroxychloroquine plus azithromycin over hydroxychloroquine alone.^{10,11} In RECOVERY, azithromycin alone (without hydroxychloroquine) did not improve survival or other clinical outcomes when compared to the usual standard of care.¹²

In addition to these randomized trials, data from large retrospective observational studies do not consistently show evidence of a benefit for hydroxychloroquine with or without azithromycin in hospitalized patients with COVID-19.¹³⁻¹⁵ Please see [Table 2b](#) or the [archived versions](#) of the Guidelines for more information.

Given the lack of a benefit seen in the randomized clinical trials, the Panel **recommends against** using hydroxychloroquine or chloroquine and/or azithromycin to treat COVID-19 in hospitalized patients **(AI)**.

Nonhospitalized Patients

Several randomized trials have not shown a clinical benefit for hydroxychloroquine in nonhospitalized patients with early, asymptomatic, or mild COVID-19.^{16,17} In an open-label trial, Mitja et al. randomized 307 nonhospitalized people who were recently confirmed to have COVID-19 to receive hydroxychloroquine or no antiviral treatment. Patients in the hydroxychloroquine arm received hydroxychloroquine 800 mg on Day 1 followed by 400 mg daily for an additional 6 days. The authors reported no difference in the mean reduction in SARS-CoV-2 RNA at Day 3 or the time to clinical improvement between the two arms (see [Table 2b](#) for more information). In another trial, treating patients who had asymptomatic or mild COVID-19 with hydroxychloroquine with or without azithromycin did not result in greater rates of virologic clearance (as measured by a negative polymerase chain reaction [PCR] result on Day 6).¹⁸

An open-label, prospective, randomized trial compared oral azithromycin 500 mg once daily for 3 days plus standard of care to standard of care alone in nonhospitalized, high-risk, older adults who had laboratory-confirmed or suspected COVID-19. No differences were observed between the arms in the primary endpoints of time to first self-reported recovery and hospitalization or death due to COVID-19. These findings remained consistent in an analysis that was restricted to participants with positive SARS-CoV-2 PCR results. The study was ultimately halted due to futility.¹⁹ Similarly, in a preliminary report from ATOMIC-2, adding oral azithromycin 500 mg once daily to standard of care for 14 days did not reduce the risk of hospitalization or death among 292 participants with mild to moderate COVID-19.²⁰

While ongoing clinical trials are still evaluating the use of chloroquine, hydroxychloroquine, and azithromycin in outpatients, the existing data suggest that it is unlikely that clinical benefits will be identified for these agents. The Panel **recommends**

against the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19 in nonhospitalized patients **(AIIa)**.

Adverse Effects

Chloroquine and hydroxychloroquine have similar toxicity profiles, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than chloroquine. Cardiac adverse events that have been reported in people who received hydroxychloroquine include QTc prolongation, Torsades de Pointes, ventricular arrhythmia, and cardiac deaths.²¹

The use of azithromycin has also been associated with QTc prolongation,²² and using it in combination with hydroxychloroquine has been associated with a higher incidence of QTc prolongation and cardiac adverse events in patients with COVID-19.^{23,24}

Drug-Drug Interactions

Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 2D6, and these drugs are also P-glycoprotein inhibitors. Chloroquine and hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.²⁵

Drug Availability

Hydroxychloroquine, chloroquine, and azithromycin **are not approved** by the Food and Drug Administration (FDA) for the treatment of COVID-19. Furthermore, the FDA Emergency Use Authorization for hydroxychloroquine and chloroquine was revoked in June 2020.

References

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www.covid19treatmentguidelines.nih.gov
An official website of the National Institutes of Health