2020

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Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

# Effect of Chloroquine, Hydroxychloroquine, and Azithromycin on the Corrected QT Interval in Patients With SARS-CoV-2 Infection

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**BACKGROUND:** The novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is responsible for the global coronavirus disease 2019 pandemic. Small studies have shown a potential benefit of chloroquine/hydroxychloroquine±azithromycin for the treatment of coronavirus disease 2019. Use of these medications alone, or in combination, can lead to a prolongation of the QT interval, possibly increasing the risk of Torsade de pointes and sudden cardiac death.

**METHODS:** Hospitalized patients treated with chloroquine/hydroxychloroquine±azithromycin from March 1 to the 23 at 3 hospitals within the Northwell Health system were included in this prospective, observational study. Serial assessments of the QT interval were performed. The primary outcome was QT prolongation resulting in Torsade de pointes. Secondary outcomes included QT prolongation, the need to prematurely discontinue any of the medications due to QT prolongation, and arrhythmogenic death.

**RESULTS:** Two hundred one patients were treated for coronavirus disease 2019 with chloroquine/hydroxychloroquine. Ten patients (5.0%) received chloroquine, 191 (95.0%) received hydroxychloroquine, and 119 (59.2%) also received azithromycin. The primary outcome of torsade de pointes was not observed in the entire population. Baseline corrected QT interval intervals did not differ between patients treated with chloroquine/hydroxychloroquine (monotherapy group) versus those treated with combination group (chloroquine/hydroxychloroquine and azithromycin; 440.6±24.9 versus 439.9±24.7 ms, $P$=0.834). The maximum corrected QT interval during treatment was significantly longer in the combination group versus the monotherapy group (470.4±45.0 ms versus 453.3±37.0 ms, $P$=0.004). Seven patients (3.5%) required discontinuation of these medications due to corrected QT interval prolongation. No arrhythmogenic deaths were reported.

**CONCLUSIONS:** In the largest reported cohort of coronavirus disease 2019 patients to date treated with chloroquine/hydroxychloroquine±azithromycin, no instances of Torsade de pointes, or arrhythmogenic death were reported. Although use of these medications resulted in QT prolongation, clinicians seldomly needed to discontinue therapy. Further study of the need for QT interval monitoring is needed before final recommendations can be made.

**VISUAL OVERVIEW:** A visual overview is available for this article.

**Key Words:** azithromycin ■ chloroquine ■ COVID-19 ■ hydroxychloroquine ■ pandemic ■ QT prolongation

In December of 2019, reports of an unknown pneumonia not responsive to traditional treatments emerged in Wuhan, China. The pathogen, which came to be identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel coronavirus that is now known to be responsible for the coronavirus disease 2019 (COVID-19) illness. Since then, the virus has spread internationally infecting ≈1 million individuals and resulting in >50 000

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For Sources of Funding and Disclosures, see page 504.



*Circulation: Arrhythmia and Electrophysiology* is available at www.ahajournals.org/journal/circep

## WHAT IS KNOWN?

- The antimalaria drugs chloroquine and hydroxychloroquine and the commonly used macrolide antibiotic azithromycin are all known to increase the corrected QT interval.
- A corrected QT interval >500 ms increases the risk of torsade de pointes by 2- to 3-fold. Other risk factors include drug interactions affecting drug serum levels, concomitant use of QT prolonging agents, female gender, structural heart disease, genetic polymorphisms, electrolyte disturbances, bradycardia, and hepatic disease.

## WHAT THE STUDY ADDS?

- In hospitalized COVID-19 patients, the use of chloroquine/hydroxychloroquine and azithromycin resulted in a significantly greater increase in the corrected QT interval when compared with monotherapy with either chloroquine or hydroxychloroquine.
- Although patients experienced corrected QT interval prolongation, especially when combination therapy was used, the risk of arrhythmic death and torsade de pointes were not increased.
- Though the efficacy of chloroquine/hydroxychloroquine±azithromycin in patients with coronavirus disease 2019 (COVID-19) is unproven, the arrhythmic risk appears to be low and may not warrant monitoring in most hospitalized patients.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **COVID-19** | coronavirus disease 2019 |
| **hERG** | human ether-à-go-go related gene |
| **MCOT** | Mobile Cardiac Outpatient Telemetry |
| **SARS-CoV-2** | severe acute respiratory syndrome coronavirus 2 |
| **TdP** | torsade de pointes |

deaths. COVID-19 was declared a public health emergency of international concern on January 30, 2020[1]. Although strong data supporting any specific therapy has been lacking, several pharmacological intervention strategies have been proposed for the management of COVID-19 in hopes of decreasing morbidity and mortality related to the illness. One such therapy currently under study in humans is the use of chloroquine or hydroxychloroquine. Chloroquine, a medication commonly used to treat malaria, has been shown to inhibit viral infection by changing the endosomal pH that is required for viral-cell fusion as well as interfering with the glycosylation of cellular receptors of SARS-CoV.[2] Compared with chloroquine, hydroxychloroquine has been shown in vitro to have higher inhibition against SARS-CoV-2.[3] These limited studies have resulted in a surge in the use of chloroquine or hydroxychloroquine with and without azithromycin in patients requiring inpatient care for COVID-19. Although many are hopeful that these inexpensive and readily available medications may be the key to decreasing mortality in this pandemic, as of the writing of this article, no such data exists. A notable concern is the association of QT prolongation and Torsade de pointes (TdP) with these medications when individually prescribed, and the increased risk when they are administered together, especially in patients with hepatic disease or renal failure. To evaluate the arrhythmic safety of chloroquine/hydroxychloroquine±azithromycin, we conducted this prospective evaluation in adult patients hospitalized with COVID-19.

## METHODS

To minimize the possibility of unintentionally sharing information that can be used to reidentify private information, a subset of the data generated, and the analytical methods used for this study are available from the corresponding author to other researchers upon reasonable request. This study was approved by the Institutional Review Board of Northwell Health, which waived the requirement for individual informed consent.

From the start of the outbreak until April 4, 2020, 3180 patients have received combination hydroxychloroquine and azithromycin, and 1181 patients received hydroxychloroquine alone for the treatment of COVID-19 in 14 hospitals of the New York State Northwell Health system. The present study is an in-depth prospective, observational study from 3 of the hospitals. All hospitalized patients >18 years of age with polymerase chain reaction confirmed COVID-19 illness treated with chloroquine/hydroxychloroquine±azithromycin were identified from March 1 to March 23. The decision to treat with chloroquine/hydroxychloroquine±azithromycin was based on the clinical decision of the admitting physician and predescribed healthcare system guidelines. Healthcare system criteria for the use of chloroquine/hydroxychloroquine±azithromycin therapy placed on March 1 were as follows: confirmed Covid-19 polymerase chain reaction testing or high suspicion of Covid-19 with test pending; acute respiratory distress syndrome or severe illness characterized by systemic inflammatory response syndrome criteria; or clinician's judgment that the patient is likely to progress to acute respiratory distress syndrome or severe illness in the next 6 hours. Patients not meeting the criteria for therapy were excluded from the study. Patients chronically on hydroxychloroquine for autoimmune diseases, such as lupus, those with a documented hypersensitivity to any of the agents, and any patient that refused the therapies were excluded from the study.

Demographics, inpatient medication lists, values from the baseline ECGs including QRS duration, QRS morphology, and QT interval duration were collected on all patients before initiation of therapy. Inpatient medication orders were reviewed daily and any concomitant QT-prolonging agent usage was identified. Twice daily ECGs, except for patients that received a Mobile Cardiac Outpatient Telemetry (MCOT) Patch (BioTelemetry, Malvern, PA), were obtained to assess the corrected QT interval (QTc). Given the large number of COVID-19 patients admitted throughout the health system and the limited amount of telemetry beds available, the MCOT patches were used to monitor for both QT prolongation and for arrhythmias in patients on nontelemetry units. MCOT

patches were preprogrammed to transmit twice daily telemetry strips for QT interval measurements. Telemetry or MCOT Patch urgent alerts were reviewed for all patients and any cardiac arrhythmias were documented. Premature discontinuation of any of the medications due to QT prolongation was also noted. All QT intervals obtained from an ECG or MCOT patch were manually measured by a physician on the research team. Lead II was utilized for the measurement of the QT interval on ECG. If the T-wave could not easily be measured in lead II, leads V6, or I were alternatively used. The end of the T-wave was defined as the tangent drawn from the steepest last limb of the T-wave to its intersection with the baseline. If a baseline BBB was present, the J-T interval was measured and 120 ms was added to obtain the QT interval duration. Bazett formula was used to calculate the corrected QT interval. Baseline QT interval measurements obtained from the MCOT patch were compared with that of the baseline ECG utilizing lead I, as the MCOT patch provides a lead I strip, to ensure accuracy. Serial ECGs were not obtained on MCOT patients to decrease staff exposure. Given the observational nature of the study, members of the research team measuring the QT interval were not blinded to the patient information or course. All telemetry, ECG, and MCOT patch monitoring findings, and QT interval measurements were adjudicated by a senior board-certified cardiac electrophysiologist and a cardiac electrophysiology fellow board-certified in cardiovascular disease.

## OUTCOME MEASURES

The primary clinical outcome of the study was QT prolongation resulting in TdP. Secondary outcomes included QT prolongation and QT prolongation that resulted in the need to prematurely terminate chloroquine, hydroxychloroquine, or azithromycin as well as arrhythmogenic death.

## STATISTICAL ANALYSIS

As this was a prospective, observational study without a specific control population, only a basic statistical analysis was utilized. Continuous variables were reported as the mean±SD and categorical variables were reported as numerical values and percentages. The Welch *t* test was used to compare ECG changes during treatment with the patients' baseline ECGs. A multivariable linear regression analysis was performed to test the impact of monotherapy versus combination therapy, and gender along with the interaction between the 2 on the outcome of change in QTc. Fisher exact test was used to compare the number of patients with a QTc >500 ms in the monotherapy versus combination groups. The SAS Version 9.4 (Cary, NC) statistical software was used for the analysis.

## RESULTS

Between March 1st and March 23, there were 201 patients that were treated for COVID-19 with either chloroquine or hydroxychloroquine at 3 hospitals in the Northwell Health system. A minority of these patients (10, 5.0%) received chloroquine. Of the 201 patients on either chloroquine or hydroxychloroquine, 119 (59.2%) also received azithromycin. The treatment regimens for these medications were as follows: chloroquine 500 mg by mouth twice daily for 1 day followed by 500 mg by mouth once daily for 4 days, hydroxychloroquine 400 mg by mouth twice daily for 1 day followed by 200 mg by mouth twice daily for 4 days, and azithromycin 500 mg by mouth or intravenous daily for 5 days. The average age of the cohort was 58.5±9.1 and 115 (57.2%) were male patients. Complete demographics are displayed in Table 1, and details regarding inpatient medication usage are outlined in Table 2.

A baseline ECG was performed before initiating therapy for COVID-19 for all patients. A majority of patients were in sinus rhythm (177, 88.1%) with baseline heart rate of 80.5±17.7 beats per minute. The mean QRS duration for the population at baseline was 92.8±19.0 ms with 46 patients (22.9%) having an intraventricular conduction delay, incomplete, or complete right bundle branch block, left bundle branch block, or a ventricular paced rhythm.

Serial ECGs were used to monitor QTc intervals for 84 patients, and 117 patients (58.2%) were monitored with an MCOT patch. The baseline QTc for the entire cohort was 439.5±24.8 ms and 8 patients (4.0%) had a baseline QTc >500 ms. The average maximum QTc during treatment for the entire cohort was 463.3±42.6 ms and the post-treatment QTc was 454.8±40.1 ms. The average increase in the QTc after the 5-day course treatment was 19.33±42.1 ms (Table 3).

The baseline QTc intervals for the monotherapy group were 438.9±25.0 ms and for the combination therapy group was 439.9±24.7 ms ($P$=0.79). The maximum QTc during treatment was significantly shorter in patients

**Table 1. Baseline Demographics**

| Characteristic | N=201 |
|---|---|
| Age, y | 58.5±9.1 |
| Male sex | 115 (57.2%) |
| Body mass index, kg/m$^2$ | 28.2±2.8 |
| Hypertension | 121 (60.2%) |
| Hyperlipidemia | 84 (41.8%) |
| Diabetes mellitus | 65 (32.3%) |
| Atrial fibrillation | 14 (7.0%) |
| Coronary artery disease | 23 (11.4%) |
| Chronic obstructive pulmonary disease/asthma | 30 (14.9%) |
| Chronic kidney disease ≥stage III | 10 (5.0%) |
| Ejection fraction, % | 61.9±5.7* |
| Heart failure | 15 (7.5%) |
| Prior permanent pacemaker/automated internal cardioverter-defibrillator | 3 (1.5%) |

Values listed are represented as means±SDs for continuous variables and numbers (percentages) for categorical variables.

*Data for ejection fraction, including echocardiograms performed within the last 6 months, was only available for 41 patients (20.4%).

**Table 2. Inpatient Medication Usage**

| Medication | N=201 |
|---|---|
| Hydroxychloroquine | 191 (95.0%) |
| Chloroquine | 10 (5.0%) |
| Azithromycin | |
| Total | 119 (59.2%) |
| 1 dose | 26 (12.9%) |
| 2–4 doses | 46 (22.9%) |
| 5 doses | 47 (23.4%) |
| Beta blocker/nondihydropyridine calcium channel blocker | 34 (16.9%) |
| Antiarrhythmic medications | 3 (1.5%) |
| Antiplatelets | 28 (13.9%) |
| Oral anticoagulants | 12 (6.0%) |
| Other QT prolonging agents* | 81 (40.3%) |

Values listed are represented as numbers (percentages) for categorical variables.

*Albuterol, alprazolam, amiodarone, amitriptyline, aripiprazole, citalopram, chlorpromazine, ciprofloxacin, clozapine, cyclobenzaprine, dexmedetomidine, diphenhydramine, donepezil, dronedarone, escitalopram, flecainide, furosemide, fluconazole, haloperidol, levetiracetam, levofloxacin, lithium, metoclopramide, mirtazapine, norepinephrine, olanzapine, ondansetron, pantoprazole, phenobarbital, quetiapine, risperidone, venlafaxine, ziprasidone

treated with chloroquine/hydroxychloroquine monotherapy when compared with patients treated with a combination of either of these medications and azithromycin (453.3±37.0 versus 470.4±45.0 ms, *P*=0.004; Table 4). Additionally, there were no statistically significant effects of gender (*P*=0.091) or an interaction between the effects of gender and medications on the difference between the Maximum QTc and the baseline QTc (*P*=0.93). The overall trajectory of QTc change is represented in Figure 1. The number of patients with a peak QTc >500 ms was 7 (8.6%) in the monotherapy group versus 11 (9.2%) in the combination therapy group (*P*=1.00) (Figure 2). Further details regarding these patients can be found in Table 5.

In addition to QT prolongation, there were 17 instances of new-onset atrial fibrillation that were discovered either on telemetry or an MCOT patch. Seven patients had monomorphic nonsustained ventricular tachycardia, and 1 patient had sustained, hemodynamically stable, monomorphic ventricular tachycardia in the setting of likely viral myocarditis (Table 6). The primary outcome of QT prolongation leading to TdP was not observed in the entire population. Arrhythmogenic death was also not observed in the entire cohort. The secondary outcome involving the need to discontinue hydroxychloroquine due to QT prolongation occurred in 7 (3.5%) patients with average QTc of 504.4±39.5 ms. Details regarding these patients can be found in Tables 7 and 8. The trajectory of their QTc change is represented in Figure 3. A complete list of arrhythmic events and interventions is listed in Table 9. Following the development and implementation of the Northwell flow chart to minimize TdP in COVID-19 inpatients on

**Table 3. Electrocardiographic Characteristics of the Study Cohort**

| ECG Characteristics | N=201 | *P* Value |
|---|---|---|
| Sinus rhythm | 177 (88.1%) | |
| Atrial fibrillation/flutter | 14 (7.0%) | |
| Baseline heart rate | 80.5±17.7 | |
| Baseline QRS | 92.8±19.0 | |
| Baseline QTc | 439.5±24.8 | – |
| Max QTc | 463.3±42.6 | <0.05 |
| Max QTc–baseline QTc | 23.8±35.5 | |
| QRS duration | 94.9±19.2 | |
| QRS duration–baseline QRS | 2.2±9.6 | |
| Final QTc | 454.8±40.1 | <0.05 |
| Final QTc–baseline QTc | 15.4±35.4 | |
| QRS duration | 95.9±20.2 | |
| QRS duration–baseline QRS | 3.0±10.5 | |

Values listed are represented as means±SDs for continuous variables. P values to assess ECG changes to the baseline ECG. QTc indicates corrected QT interval.

hydroxychloroquine/azithromycin, lidocaine was used to facilitate continuation of hydroxychloroquine in 2 other patients.[4] The first patient's QTc increased from baseline of 458 to 594 ms after receiving hydroxychloroquine 400 mg for 2 doses followed by 200 mg for 3 doses and 2 doses of intravenous azithromycin 500 mg. The patient was given a single dose of intravenous lidocaine 100 mg, which improved QTc to 479 ms. Azithromycin was discontinued at this time while hydroxychloroquine 200 mg twice daily was continued for the full 5-day course. Of note, this patient was given a dose of intravenous amiodarone 150 mg 2 days before reaching the peak QTc during a rapid

**Table 4. Comparison of QTc Measurement in HCQ Cohort vs HCQ and AZM Cohort**

| | QTc Measurements in Patients Treated With HCQ/CQ (N=82) | QTc Measurements in Patients Treated With HCQ/CQ and AZM (N=119) | *P* Value |
|---|---|---|---|
| Baseline QTc | 438.9±25.0 | 439.9±24.7 | 0.79 |
| Baseline QRS | 92.0±15.5 | 93.0±19.8 | 0.85 |
| Max QTc | 453.3±37.0 | 470.4±45.0 | 0.004 |
| Max QTc–baseline QTc | 14.4±25.0 | 30.4±40.2 | <0.001 |
| QRS duration | 91.9±15.6 | 95.6±20.0 | 0.48 |
| QRS duration–baseline QRS | −0.1±6.14 | 2.7±10.2 | 0.21 |
| QTc >500 (no. of patients) | 7 | 11 | 1.00 |
| Final QTc | 444.7±34.2 | 462.0±42.4 | 0.002 |
| Final QTc–baseline QTc | 6.0±25.0 | 22.0±40.1 | <0.001 |
| QRS duration | 91.9±13.1 | 96.7±21.4 | 0.30 |
| QRS duration–baseline QRS | −0.2±8.5 | 3.7±10.8 | 0.18 |

Values listed are represented as means±SDs for continuous variables. AZM indicates azithromycin; CQ, chloroquine; HCQ, hydroxychloroquine; QTc, corrected QT; and Max, maximum.

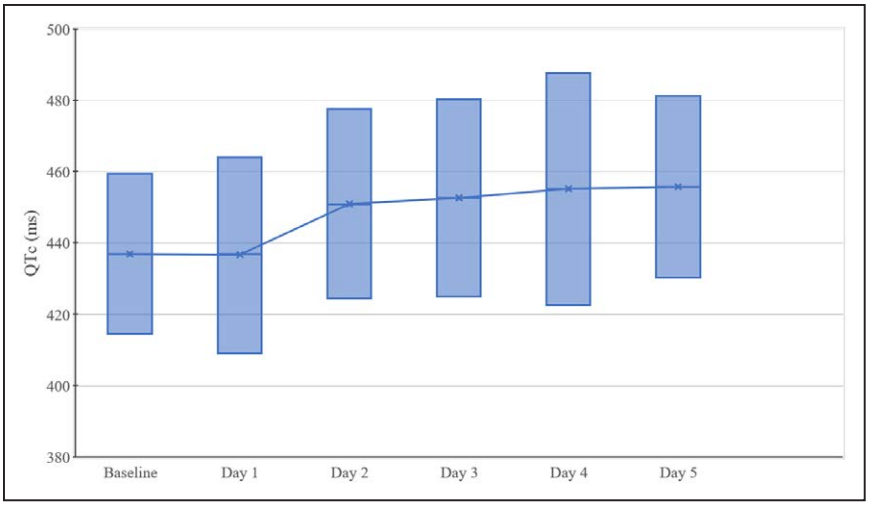


**Figure 1. Trajectory of corrected QT interval (QTc) change in 201 patients receiving hydroxychloroquine±azithromycin.**
Change in QTc was seen starting on day 2 of therapy with max QTc being reached on day 4 by the majority of patients.

response for atrial fibrillation and acute hypoxic respiratory failure that required intubation. Two days after finishing the course of hydroxychloroquine, the QTc prolonged to 601 ms. Of note, the patient was receiving intravenous furosemide and pantoprazole, which may have contributed to the QTc prolongation. The patient appropriately responded to another dose of intravenous lidocaine. The subsequent QTc improved to 551 mg and normalized to <500 ms on subsequent ECGs. The second patient's QTc increased from 456 ms to 620 ms after receiving 1 dose of hydroxychloroquine. She was given a dose of intravenous lidocaine 100 mg, which improved the QTc to 550 ms. This patient went on to complete the 5-day course of hydroxychloroquine with no further prolongation of QTc.

## DISCUSSION

The main findings of this study were (1) the use of chloroquine/hydroxychloroquine and azithromycin led to a significantly greater increase in the corrected QT interval when compared to monotherapy with either chloroquine or hydroxychloroquine, (2) prolongation of the QTc only led to premature discontinuation of these medications in 3.5% of patients, and (3) there were no instances of the primary end point of TdP in the entire cohort.

The SARS-CoV-2 virus is an enveloped β coronavirus that is thought to have transmitted to humans via zoonotic transfer.[5,6] Virus binding and cell entry are facilitated by a type I membrane spike glycoprotein on the surface of the SARS-CoV-2 virus that binds to ACE (angiotensin-converting enzyme)-2 receptors found in the upper and lower human respiratory tract.[7,8] The SARS-CoV-2 virus emerged from China in December of 2019 and has subsequently resulted in an explosion of proposed therapies for treating the virus. Among these therapies, chloroquine/hydroxychloroquine with and without azithromycin are now commonly being used, following studies that showed virus-cell fusion inhibition.[2,3] To date, there has been little actionable clinical data on the efficacy of using these medications in humans infected with the SARS-CoV-2 virus. In a 2005 cohort of 23 hospitalized patients with SARS-CoV, To et al[9] reported a direct correlation between viral load and increasing age, suggesting an increased expression of ACE-2 receptors with age may result in higher viral loads. The relationship between viral load and disease severity, however, was not addressed. Viral load was noted to peak during the first week of

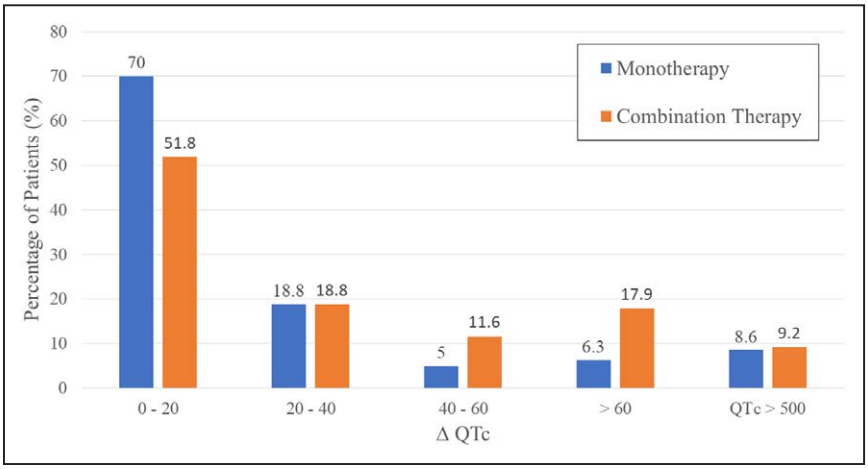


**Figure 2. Percentage of patients with increase in corrected QT interval (QTc) for HCQ monotherapy vs hydroxychloroquine and azithromycin combination therapy.**
The majority of patients in both groups had an increase in QTc of 0–20 ms. Higher percentage of patients treated with the combination therapy had an increase in QTc of 40–60 ms and >60 ms.

**Table 5. Characteristics of Patients With QTc >500 ms**

| | QTc >500 ms in Patients Treated With HCQ/CQ (n=7) | QTc >500 ms in Patients Treated With HCQ/CQ and AZM (n=11) | *P* Value |
|---|---|---|---|
| Female sex | 3 | 3 | 0.63 |
| Structural heart disease | 1 | 0 | 0.39 |
| Cirrhosis | 0 | 0 | 1.00 |
| Baseline QTc, ms | 456.5±21.2 | 449.7±24.4 | 0.578 |
| Receiving other QT-prolonging medications | 3 | 7 | 0.63 |

AZM indicates azithromycin; CQ, chloroquine; HCQ, hydroxychloroquine; and QTc, corrected QT.

illness and steadily declined over the following week.[10] Subsequently, a 30-patient study in mildly symptomatic patients showed no benefit of chloroquine with regards to clearance of viral load, time to temperature normalization, and disease progression.[11] Major trials evaluating clinical efficacy of this combination therapy are currently underway globally.

A major concern with the use of this therapy has been the risk of QT prolongation and TdP. TdP is a form of polymorphic ventricular tachycardia that occurs in the setting of QT prolongation that is characterized by gradual twisting and amplitude change of the QRS complexes around an isoelectric line that either spontaneously terminates or degenerates to ventricular fibrillation in about 10% of cases.[12,13] Traditionally, QT-prolonging agents have been avoided in individuals with a QTc >500 ms due to a 2-fold to 3-fold increase in risk for TdP with such intervals.[14–16] Most drugs cause QT prolongation by blocking the human ether-à-go-go related gene (*hERG*) potassium channel, the voltage-gated ion channel that mediates the rapid component of the delayed rectifier potassium current, $I_{Kr}$, resulting in lengthening of both ventricular repolarizations, and the duration of the ventricular action potential.[17] In a similar fashion, this can result in the reactivation of calcium influx causing triggered early afterdepolarization activity. A well-timed early afterdepolarization trigger, in the presence of a prolonged QT interval, can result in TdP.[18]

Other risk factors for TdP include drug interactions affecting drug serum levels, concomitant use of QT-prolonging agents, female sex, structural heart disease, genetic polymorphisms, electrolyte disturbances, bradycardia, and hepatic disease. Such risk factors result in repolarization reserve reduction.[18,19] Although the QTc is sensitive for predicting TdP, it is not specific. The relationship between QT prolongation and TdP is not linear as drugs that prolong the QT have not consistently been associated with cardiac arrhythmias. Incidences of sudden cardiac death occurring in the absence of QT prolongation on surface ECG have also been reported. Of all the QT prolonging drugs, antiarrhythmics have the highest risk of TdP with an incidence of 1% to 5%, whereas the risk from noncardiovascular drugs is much lower at 0.001%.[13]

Four hundred million courses of antimalarial drugs are annually used around the world.[20] Antimalarial drugs are well known for their potential cardiac toxicity and QT prolongation effects. Of the drugs used, quinidine and halofantrine are the most likely to cause QT prolongation and TdP.[21–23] Chloroquine's reported risk of sudden cardiac death is limited to cases of hypotension due to vasodilation and negative inotropy resulting from rapid parenteral administration of the medication or situations of self-inflicted overdose.[24] The risk of QT prolongation and

**Table 6. Characteristics of Patients With Monomorphic Ventricular Arrhythmias**

| Age/ sex | Medication Regimen | Arrhythmia Duration, s | Arrhythmia Rate (beats per minute) | CAD | HF | EF (%) | Evidence of Ischemia/ Myocarditis | HS Trop, ng/L | K, mmol/L | Mg, mg/ dL | $Ca^{2+}$, mg/dL | Clinical Status | Outcome (Length of Stay in Days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49M | HCQ | 240 | 200 | 0 | 1 | 40 | Myocarditis | 4407 | 4.8 | 2.1 | 8.8 | ICU/ ventilator | Deceased* (5) |
| 58M | HCQ+AZM | 5.6 | 180 | 0 | 1 | 15 | No | 57 | 3.5 | 2.0 | 8.7 | Room air | Discharged (2) |
| 65M | HCQ+AZM | 12 | 195 | 0 | 0 | 58 | No | 28 | 3.7 | 2.0 | 9.4 | Nasal cannula | Discharged (14) |
| 85M | HCQ+AZM | 10 | 190 | 0 | 0 | … | No | 44 | 4.0 | 2.9 | 8.4 | ICU/ ventilator | Deceased* (22) |
| 56F | HCQ+AZM | 5 | 170 | 0 | 0 | … | No | 67 | 5.5 | 2.7 | 10.1 | ICU/ ventilator | Admitted (24) |
| 88F | HCQ+AZM | 20 | 210 | 0 | 0 | … | No | 50 | 3.7 | 2.5 | 8.4 | Nasal cannula | Discharged (13) |
| 72F† | HCQ | 3.6 | 180 | 0 | 0 | … | No | 23 | 4.2 | 1.8 | 10.1 | Nasal cannula | Discharged (11) |
| 69M† | HCQ+AZM | 1.6 | 150 | 0 | 0 | … | No | 15 | 3.5 | 2.1 | 8.7 | Nasal cannula | Discharged (6) |

AZM indicates azithromycin; $Ca^{2+}$, calcium; CAD, coronary artery disease; EF, ejection fraction; F, female; HCQ, hydroxychloroquine; HF, heart failure; HS, high sensitivity; ICU, intensive care unit; K, potassium; M, male; MCOT, Mobile Cardiac Outpatient Telemetry; Mg, magnesium; and Trop, troponin.

*The cause of death for these patients was multi-system organ failure.

†These patients were monitored with MCOTs. The remainder were monitored with 12-lead electrocardiograms.

**Table 7. Proportion of Patients With Max QTc That Continued vs Discontinued Medical Therapy With HCQ±AZM**

| Max QTc, ms | Total Patients on HCQ±AZM With QTc >500 ms | Number of Patients Whose HCQ±AZM Was Discontinued Due to QTc >500 ms |
|---|---|---|
| 500–520 | 8 | 2 |
| 520–540 | 2 | 0 |
| 540–560 | 3 | 1 |
| 560–580 | 2 | 1 |
| 580–600 | 2 | 2 |
| >600 | 1 | 1 |

AZM indicates azithromycin; HCQ, hydroxychloroquine; and QTc, corrected QT interval.

TdP with hydroxychloroquine is limited to a series of case reports in patients with either chronic use or overdose.[25–27]

The reported effects of chloroquine and hydroxychloroquine on the QT interval may also be significantly affected by the course of acute malaria. Increased sympathetic tone due to fevers, anxiety, and anorexia at the onset of illness results in QT interval shortening. As patients recover with medical therapy, QT interval normalizes. QT interval normalization on day 3 of therapy, which coincides with peak drug level, may have been mistakenly attributed to the drugs.[24] Furthermore, the Bazett formula, used in malaria studies, overestimates the number of patients with QT prolongation and could have contributed to the reported QT prolonging effects of chloroquine and hydroxychloroquine.[28]

Azithromycin, a widely utilized macrolide antibiotic, has been reported to increase QT interval and incidence of TdP.[29–35] In a 2012 retrospective observational study, 5 days of therapy with azithromycin was found to have a small but statistically significant increase in cardiovascular death driven by sudden cardiac death. This effect did not persist after the treatment was stopped.[36] The proarrhythmic mechanism of azithromycin is thought to be due to the drug's ability to increase cardiac sodium current and promote intracellular sodium loading.[37] However, data are lacking to show that the increased risk of death with azithromycin is a result of QT prolongation and TdT. Moreover, azithromycin and chloroquine combination therapy has been used for the protection against malaria and sexually transmitted infections in pregnant women with no reports of syncope or sudden cardiac death.[38]

Our study revealed that in the entire cohort treated with chloroquine/hydroxychloroquine or azithromycin, the increase in QTc to its peak (max QTc), and post-treatment QTc (final QTc) were statistically significant ($P<0.05$; Table 3). When further broken down to 2 treatment cohorts as shown in Table 4, the group treated with the combination therapy had longer Max and Final QTc intervals compared with the monotherapy group ($P=0.004$ and $P=0.002$, respectively). However, it is important to highlight that no patient had QTc prolongation that resulted in TdP. Seven patients (3.5%) needed to discontinue the medications due to QTc prolongation. Two additional patients were treated with intravenous lidocaine that shortened the QTc allowing for continuation of hydroxychloroquine. The decision to discontinue therapy was variable based on provider personal threshold and comfort. This explains why some patients with similarly prolonged QTc intervals continued therapy.

As the volume of hospitalized COVID-19 patients has increased throughout our health system, our ability to monitor every patient receiving combination therapy became limited due to the finite amount of telemetry beds available. The use of MCOT patch monitors allowed us to expand remote monitoring of cardiac arrhythmias and QT prolongation in patients not on traditional telemetry.

**Table 8. Characteristics of Patients With Discontinued HCQ±AZM due to QT Prolongation**

| Age/ Sex | Medication Regimen | Baseline QTc | Max QTc | Other QT Prolonging Meds | CAD | HF | EF, % | Evidence of Ischemia/ Myocarditis | HS Trop, ng/L | K, mmol/L | Mg, mg/dL | $Ca^{2+}$, mg/dL | Clinical Status | Outcome (Length of Stay in Days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 71M | HCQ+AZM | 410 | 546 | Amiodarone | 1 | 0 | … | No | 29 | 5.0 | 2.5 | 9.2 | ICU/ventilator | Deceased* (9) |
| 47F | HCQ | 442 | 483 | Haloperidol, Clozapine | 0 | 0 | … | No | 16 | 3.7 | 1.9 | 8.6 | Room air | Discharged (11) |
| 49M | HCQ+AZM | 471 | 617 | … | 0 | 0 | … | No | 11 | 3.7 | 2.8 | 9.2 | ICU/ventilator | Admitted (25) |
| 67M | HCQ+AZM | 434 | 501 | Dronedarone, Pantoprazole | 0 | 0 | … | No | … | 3.7 | 2.3 | 8.7 | Nasal cannula | Discharged (10) |
| 83F | HCQ+AZM | 444 | 588 | … | 1 | 1 | 30 | No† (Takotsubo) | 400 | 4.0 | 2.7 | 9.1 | ICU/ventilator | Deceased* (22) |
| 45M | HCQ+AZM | 458 | 572 | … | 0 | 0 | … | No | 13 | 4.2 | 2.4 | 9.1 | ICU/ventilator | Admitted (24) |
| 56M‡ | HCQ | 469 | 565 | Pantoprazole | 0 | 0 | … | No | 16 | 3.9 | 2.2 | 8.8 | Nonrebreather | Discharged (14) |

AZM indicates azithromycin; $Ca^{2+}$, calcium; CAD, coronary artery disease; EF, ejection fraction; F, female; HCQ, hydroxychloroquine; HF, heart failure; HS, high sensitivity; ICU, intensive care unit; K, potassium; M, male; MCOT, Mobile Cardiac Outpatient Telemetry; Mg, magnesium; QTc, corrected QT interval; and Trop, troponin.

*The cause of death was hypoxic respiratory failure and sepsis for both patients.

†A transthoracic echocardiogram performed during the admission showed apical and mid left ventricular hypokinesis with sparing of the basal segments.

‡This was the only patient that monitored with an MCOT. The remainder were monitored with 12-lead electrocardiograms.

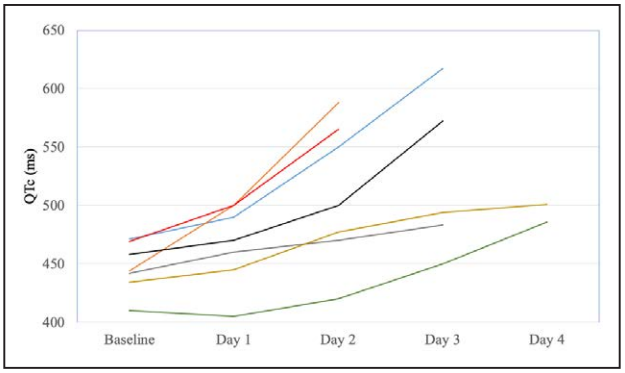


**Figure 3. Trajectory of corrected QT interval (QTc) changes for patients whose hydroxychloroquine (HCQ)±azithromycin (AZM) was discontinued due to QT prolongation (n=7).**
The majority of the patients that had their HCQ±AZM therapy discontinued reached a max QTc >500 ms. Decision to discontinue therapy was based on clinician preference.

The MCOT monitor is Food and Drug Administration–approved for the measurement, analysis, and reporting of QT intervals. The use of the monitor resulted in a reduction of exposures and personal protective equipment use by healthcare workers as the need for serial ECGs to monitor the QT interval was eliminated in this subset of patients.

Further investigation of this combination therapy is needed, especially given the lack of randomized controlled trials showing efficacy. Based on our experience, although patients experience QTc prolongation, especially when combination therapy is used, the risk of arrhythmic death or TdT were not increased. Furthermore, to date, a total of 3180 patients have received combination hydroxychloroquine and azithromycin, and 1181 patients received hydroxychloroquine alone for the treatment of COVID-19 in our healthcare system. There continues to be no reports of TdT in those patients. In short, the use of this combination therapy for a period of 5 days may not warrant monitoring for cardiac arrhythmias in most patients. Our Infection disease team is no longer recommending the addition of azithromycin. Coupled with the findings in this study, we have simplified our approach to monitoring patients on therapy. If the baseline QTc is ≤500 ms (550 if bundle branch block or QRS duration >120 ms) no monitoring or serial ECGs will be required. If the baseline QTc is >500 ms (550 if bundle branch block or QRS duration >120 ms) on telemetry or MCOTs, no serial ECGs will be utilized for arrhythmia and QTc monitoring. We will be performing a prospective analysis of this approach.

## Limitations

The main limitation of this study is the absence of a control cohort of patients with COVID-19 infections that were not treated with any of these medications. Although this would have provided a stronger analysis, nearly every hospitalized patient with COVID-19 received ≥1 of these medications during the course of their admission during this study period. The number of patients with underlying cardiac disease in the study is small, potentially limiting generalizability to that population. The study is subject to the same limitations as other observational studies. Although baseline QT interval readings on MCOT were correlated to the baseline ECGs, subsequent QT intervals in the MCOT subset obtained while on therapy were not. This fact and the difference in filtering in MCOT patches versus traditional 12-lead ECG are a limitation. Over 4000 patients across the 17 hospitals in the Northwell Health system have received one or both therapies as of April 4, 2020 with no reported instances of TdT. This statistic, although very encouraging, may be subject to reporting bias. Lastly, our cohort of 201 patients, from the initial phases of this pandemic, represents a small fraction of the total patients we have treated. Further work is needed to confirm our findings in an even larger group of patients.

**Table 9. Arrhythmic Events and Interventions Due to QTc Prolongation**

| Arrhythmic Events and Interventions | N=201 |
|---|---|
| New-onset atrial fibrillation | 17 (8.5%) |
| Nonsustained, monomorphic ventricular tachycardia | 7 (3.5%) |
| Sustained, monomorphic ventricular tachycardia | 1 (0.5%) |
| Torsade de pointes | 0 |
| Arrhythmogenic death | 0 |
| Use of lidocaine for QTc >500 ms | 2 (0.9%) |
| Hydroxychloroquine±azithromycin discontinued due to QTc prolongation* | 7 (3.5%) |

QTc indicates corrected QT interval.
*Values listed are represented as numbers (percentages) for categorical variables.

## Conclusions

This is the largest reported cohort to date of patients with COVID-19 that were treated with chloroquine/hydroxychloroquine with and without azithromycin. We observed a marked increase in the QT intervals of these patients during treatment, that was more pronounced in patients treated with combination therapy. Despite this increase, very few patients had the medications discontinued prematurely due to QT prolongation. Most importantly, there were no cases of torsade de pointes or arrhythmic death in the entire population. Further study of the need for QT interval monitoring is needed before final recommendations can be made.

## ARTICLE INFORMATION

Received April 5, 2020; accepted April 28, 2020.

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## Acknowledgments

We thank the clinical pharmacists Rubiya Kabir, Thien Doan, and Christine Garibotto for their assistance with the data acquisition.

## Sources of Funding

None.

## Disclosures

None.

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