Urgent Guidance for Navigating and Circumventing the QTc Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for COVID-19

Running Title: Possible COVID-19 Pharmacotherapies and QTc/TdP Liability

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Abbreviations and acronyms: ACE2, angiotensin converting enzyme 2; COVID-19, coronavirus disease 19; DI-SCD, drug-induced sudden cardiac death; DI-TdP, drug-induced torsades de pointes; ECG, electrocardiogram; FDA, Food and Drug Administration; LQTS, long QT syndrome; PPE, personal protective equipment; QTc, heart rate-corrected QT interval; and SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

Keywords: COVID-19, hydroxychloroquine, long QT syndrome, QT interval, and sudden cardiac death.

ABSTRACT

As the COVID-19 global pandemic rages across the globe, the race to prevent and treat this deadly disease has led to the "off label" re-purposing of drugs such as hydroxychloroquine and lopinavir/ritonavir with the potential for unwanted QT interval prolongation, and a risk of drug-induced sudden cardiac death. With the possibility that a significant proportion of the world's population could receive soon COVID-19 pharmacotherapies with torsadogenic potential for therapy or post-exposure prophylaxis, this document serves to help healthcare providers mitigate the risk of drug-induced ventricular arrhythmias while minimizing risk to personnel of COVID-19 exposure and conserving the limited supply of personal protective equipment.

INTRODUCTION

Since its emergence from the Wuhan province of China in late 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19) respiratory illness, has claimed the lives of >20,000 individuals worldwide already.[1, 2] With the number of COVID-19 cases and deaths rising with each passing day, there is perhaps no more pressing need in medicine than to identify safe and efficacious therapies to prevent SARS-CoV-2 infections as well as to attenuate the severity of the resulting COVID-19 respiratory illness.[2] Although there are no Food and Drug Administration (FDA)-approved drugs to prevent or treat COVID-19, a number of promising novel (i.e. remdesivir) and re-purposed (i.e. hydroxychloroquine, potentially together with azithromycin) pharmacologic agents, shown to inhibit the growth of SARS-CoV-2 *in vitro*[3, 4], are being evaluated in randomized clinical trials.

In advance of more definitive evidence, clinicians on the frontlines of the pandemic have begun to use these medications under "off label" or "compassionate use" circumstances with anecdotal success.[5, 6] In light of i) the need for this practice to continue in the absence of viable, evidence-based therapies and ii) the proclivity of many promising COVID-19 pharmacotherapies -- specifically antimalarial agents such as hydroxychloroquine -- to prolong the heart rate-corrected QT interval (QTc), thereby increasing the risk of drug-induced torsades de pointes (DI-TdP), and drug induced-sudden cardiac death (DI-SCD), this document was assembled to help providers safely use these medications and minimize concomitant risks.

The pharmacodynamics and QTc prolonging/torsadogenic potential of the antimalarial medications chloroquine and hydroxychloroquine

Chloroquine and its analog hydroxychloroquine have been used for nearly 80 years as prophylactic pharmacotherapies for malaria. Although still used as antimalarial agents in parts of the world with chloroquine-sensitive *Plasmodium falciparum* protozoa, hydroxychloroquine has found new life as a disease-modifying anti-rheumatic drug for the management of conditions such as systemic lupus erythematous and rheumatoid arthritis.

At the cellular level, these antimalarial drugs accumulate in intracellular vesicles such as endosomes and lysosomes where they are protonated, leading to increased vesicular pH.[7] This in turn inhibits the activity of the pH-dependent proteases involved in the intracellular processing of secretory proteins with a number of immunological and non-immunological effects, including tumor necrosis factor α and interleukin 6.[7] Collectively, a reduction in these secretory proteins is believed to result in i) the accumulation of cytoxic heme that poisons *Plasmodium falciparum* protozoa and ii) modulation of immune cell behavior in a manner that attenuates inflammatory processes.[7]

In addition, chloroquine and hydroxychloroquine possess antiviral properties *in vitro*.[3, 4, 7, 8] Both chloroquine and hydroxychloroquine are believed to act on the entry and post-entry stages of SARS-CoV and SARS-CoV-2 infection, likely via effects on endosomal pH and the resulting under-glycosylation of angiotensin converting enzyme 2 (ACE2) receptors that are required for viral entry.[3, 4, 8]

Based on this *in vitro* data, it has been hypothesized that hydroxychloroquine, more so than chloroquine, may have therapeutic efficacy in the COVID-19 pandemic by i) preventing SARS-CoV-2 infection by inhibiting ACE2-mediated viral entry (i.e. pre-infection prophylaxis)

and ii) attenuating the post-viral cytokine storm observed in severe COVID-19 cases via a multitude of immunomodulatory mechanisms (i.e. treatment of active infection/post-viral sequelae). Promising *in vitro* data[3, 4] as well as anecdotal *in vivo* evidence of therapeutic benefit[5] have led many institutions, including Mayo Clinic, to consider the use of hydroxychloroquine as a first-line COVID-19 pharmacotherapy for the time being and spurred an array of clinical trials designed to assess the efficacy of re-purposed hydroxychloroquine in both the prevention and treatment of COVID-19.

Although the collective safety profiles of chloroquine and hydroxychloroquine are relatively favorable, both drugs block the *KCNH2*-encoded hERG/Kv11.1 potassium channel and can prolong potentially the QTc. In at-risk individuals, these so-called hERG-blockers can precipitate DI-TdP or worse, DI-SCD, especially with chronic use (**Table 1**). As a result, the number of DI-SCDs attributable to hydroxychloroquine in particular is not trivial (**Table 1**). With the theoretical possibility that a significant proportion of the world population could receive hydroxychloroquine as first-line prophylaxis or treatment, including an estimated 3 million individuals with congenital long QT syndrome (LQTS), the number of hydroxychloroquine-mediated DI-SCDs could rise precipitously unless appropriate QTc monitoring algorithms are instituted. This risk of DI-SCD could be further amplified if multiple medications, each with their own QTc prolonging/torsadogenic potential (i.e. chloroquine/hydroxychloroquine plus azithromycin and/or lopinavir/ritonavir), are used in combination (**Table 1**).

Mitigating the potential risk of DI-TdP and DI-SCD associated with widespread use of chloroquine/hydroxychloroquine in the COVID-19 pandemic

Although some might argue that DI-SCDs in the setting of widespread chloroquine/hydroxychloroquine use represents acceptable "friendly-fire" in the war on SARS-CoV-2/COVID-19, we believe that with the institution of a few simple and safe precautions, the risk of DI-TdP and DI-SCD can be mitigated. Ultimately, this comes down to identifying the small subset of individuals who, either secondary to an underlying genetic predisposition (such as congenital LQTS which is present in 1 out of 2000 people) and/or by virtue of the presence of multiple modifiable and non-modifiable QTc risk factors (**Table 2**)[9], have excessive baseline QTc prolongation (QTc $\geq$ 500 ms) and/or have an inherent tendency to develop an exaggerated QTc response (i.e. ΔQTc $\geq$ 60 ms) following exposure to medications with the unwanted side effect of potential QTc prolongation (**Figure 1**). Although the percentage of individuals at risk is small, given the pandemic nature of COVID-19, in absolute terms the number of individuals potentially at risk for lethal drug side effects is large (at least 4000 individuals out of the > 400,000 COVID-19-positive patients worldwide are expected to be at increased risk for DI-TdP/DI-SCD if treated with these medications). This would be especially true if these medications are adopted for post-exposure prophylaxis.

Traditionally, the QTc is calculated from either lead II or V_5 of the 12-lead ECG and corrected for heart rate using Bazett's or Fredericia's formula before any intra-individual or inter-individual QTc comparisons are made. Unfortunately, in the context of the COVID-19 pandemic, acquisition of the patient's QTc by the 12-lead electrocardiogram (ECG), which requires additional personnel exposure (i.e. ECG technician), and a necessity for serial ECGs, which requires exposure of complex equipment (multiple ECG wires), could further strain the

already limited supply of personal protective equipment (PPE) in many countries. Alternatively, some FDA-approved consumer mobile ECG devices are capable of generating accurate QTc measurements.[10] To this end, AliveCor just received emergency clearance from the FDA for use of the KardiaMobile-6L device (FDA-approved for atrial fibrillation detection) for QTc monitoring of COVID-19 patients treated with QT prolonging medications such as chloroquine/hydroxychloroquine (March 20, 2020, 1:15 PM CST). Similarly, many telemetry systems are equipped with real time QTc monitoring features which could be used for hospitalized patients.

For COVID-19 patients about to be treated with medications with the increased potential for DI-TdP/DI-SCD (**Figure 1**), baseline QTc status should be obtained either by a traditional 12-lead ECG or perhaps preferably with the use of a smartphone-enabled mobile QTc meter using the simple infection control measures outlined in **Figure 2** to limit personnel exposures and conserve critical PPE. On average, the QTc values for otherwise healthy post-pubertal males and females are around 410 ms and 420 ms, respectively. In contrast, a QTc value that exceeds the 99th percentile value for otherwise healthy individuals (i.e. 460 ms in both sexes before puberty, 470 ms in postpubertal males, and 480 ms in postpubertal females), in the absence of any exogenous QTc-aggravating factors, may signal an individual at increased risk for QT-related ventricular arrhythmias.[11, 12] In contrast and as a frame of reference, the average QTc value was 470 ms for the > 1400 patients with congenital LQTS who have been cared for in Mayo Clinic's Windland Smith Rice Genetic Heart Rhythm Clinic. Furthermore, with very few exceptions (amiodarone being one), patients with a resting QTc ≥ 500 ms, whether secondary to congenital LQTS or acquired (QTc prolonging drugs, QTc prolonging electrolyte abnormalities

such as hypokalemia, or QTc prolonging disease states as detailed in **Table 2**) have a significantly greater risk for both DI-TdP and DI-SCD.[13-15]

Accordingly, the baseline QTc value can be used to roughly approximate the patient's risk of DI-TdP/DI-SCD following initiation of a medication with QTc prolonging potential. For those COVID-19 patients with QTc values less than the 99th percentile for age/gender (i.e. 460 ms in pre-pubertal males/females, 470 ms in postpubertal males, and 480 ms in postpubertal females, **Figure 1** "Green-Light Status"), the risk of DI-TdP/DI-LQTS is low and chloroquine/hydroxychloroquine (or other QTc prolonging COVID-19 pharmacotherapies) should be initiated without delay as outlined in the QTc monitoring algorithm. Remember, whether by 12-lead ECG, telemetry, or smartphone-enabled acquisition of the ECG, if the noted QT interval is < than ½ the preceding RR interval, then the calculated QTc will always be < 460 ms and the patient can be "green light go" for COVID-19 treatments that may have QTc prolonging potential.

In contrast, those COVID-19 patients with a baseline QTc ≥ 500 ms are at increased risk for DI-TdP/DI-SCD (**Figure 1** "Red Light Status') and every effort should be made to i) assess and correct for contributing electrolyte abnormalities (hypocalcemia, hypokalemia, and/or hypomagnesemia), ii) review and discontinue other unnecessary QTc prolonging medications if present or transition to alternatives with less QTc liability, and/or iii) proceed with closer monitoring (telemetry) or even consideration of more significant countermeasures such as equipping the patient with a wearable defibrillator (LifeVest^{TM}, for example) if the decision is made to commence therapy.

In the setting of a QTc value ≥ 500 ms, navigating and circumventing this QTc liability depends greatly on the risk-benefit calculus and the decision rests with the treating clinician and

patient. For example, in younger COVID-19 patients (i.e. < 40 years of age) with only mild symptoms and a QTc ≥ 500 ms, it may be reasonable to avoid treatment altogether as the arrhythmia risk may outweigh the risk of developing COVID-19-related acute respiratory distress syndrome. However, in COVID-19 patients with a QTc ≥ 500 ms presenting with progressively worsening respiratory symptoms or at greater risk (i.e. > 65 years of age, immunosuppressed, and/or high risk co-morbid conditions) for respiratory complications, the potential benefit of QTc-prolonging COVID-19 pharmacotherapies may exceed the arrhythmia risk. Therefore, the ultimate goal of QTc surveillance in the COVID-19 pandemic should **NOT** be to identify those who cannot receive these medications, but to identify those with compromised or reduced 'repolarization reserve' in whom increased QTc countermeasures can and should be taken to mitigate the risk of drug-related death from DI-TdP/DI-SCD.[16]

Ultimately, much of the risk-benefit calculus awaits determination of the therapeutic efficacy of hydroxychloroquine, with or without concomitant azithromycin. Until such information is available, if the decision has been made to treat a patient with a red-light designation (**Figure 1**) based on their baseline QTc ≥ 500 ms, it seems prudent to start with hydroxychloroquine alone, rather than combination drug therapy with azithromycin. In addition, if combination drug therapy, with hydroxychloroquine and azithromycin, was started in a patient with initial green-light/yellow-light QTc status, and he or she transitions to red-light after declaring himself/herself as a "QTc reactor" with a ΔQTc ≥ 60 ms, then consideration should be given to discontinuing azithromycin, optimizing electrolyte status, or intensifying countermeasures further (placing on telemetry for continuous rhythm assessment).

Frequency of QTc Surveillance and Adjustments in the Setting of Wide QRS

Ideally, following a baseline QTc assessment, therapy may be initiated with either QTc reassurance [low risk for the vast majority (90%) of patients] or varying QTc countermeasures in place for those flagged at increased risk. The timing of on-therapy QTc surveillance will be dictated by not only the pharmacokinetics of the COVID-19 therapies used but also by the practical logistics of an institution's method of QTc monitoring. For the 12-lead ECG approach, if QTc surveillance is deemed important, then one machine should be designated for acquisition of the data and a limited number of ECG technicians/personnel should be used to minimize PPE utilization and personnel exposure. Also, the number of on-therapy QTc assessments should be constrained to minimize personnel exposure risk and PPE consumption. In this scenario, for those placed in "red light" status because their baseline QTc $\geq$ 500 ms, an initial on-therapy QTc should be obtained around 2-4 hours after the first dose and then again at 48 hours and 96 hours, respectively following treatment initiation. Patients receiving either "green light" or "yellow light" can probably forego the acute QTc assessment and wait until 48 hours and 96 hours for their on-drug QTc determination. If the on-therapy QTc is $\geq$ 500 ms or the patient has declared himself/herself to be a 'QTc reactor' with a ΔQTc $\geq$ 60 ms, then the QTc countermeasures need to be re-examined or the medications stopped in an effort to neutralize the increased potential for DI-TdP and DI-SCD (**Figure 1**).

In contrast, for those medical centers able to implement the FDA emergency-approved, smart phone-enabled approach (**Figure 2**) or determine the QTc from the telemetry strips, then that would not only eliminate ECG technician exposure risk and consumption of PPE by those individuals, but the patient's QTc could be obtained by the health care team present already, and the QTc could be obtained per shift, for example, as another "vital sign".[17] Such increased QTc

surveillance would enable discovery of the 'QTc reactor' sooner, implementation of countermeasures sooner, and would thereby hopefully circumvent the potentially preventable tragedy of DI-SCD (**Figure 1**).

Finally, for patients with a wide QRS from either ventricular pacing or right/left bundle branch block, a wide-QRS QTc adjustment will need to be made. Otherwise, patients will receive a "red light" signal inappropriately thereby resulting in therapy delay, discontinuation, or avoidance of the COVID-19 treatment altogether. In this setting, the simplest approach is to maintain the previously indicated QTc green-, yellow-, and red-light thresholds, and apply a simple formula to account for the wide QRS [wide QRS adjusted QTc = QTc – (QRS – 100 ms)]. For example, if a patient's left bundle branch block has yielded a QRS of 200 ms, and a QTc of 520 ms, this would appear to activate the red-light pathway (**Figure 1**). However, the wide-QRS adjusted QTc would be 520 ms – [200 – 100 ms] = 520 – 100 = 420 ms. Not red-light at all, but green light go with much QTc reassurance that the patient is at low risk for DI-SCD.

CONCLUSIONS

As this coronavirus pandemic continues to spread and wreak havoc, economic loss, and more importantly the tragic deaths of thousands throughout the world, we must all do our part in this war on COVID-19. Washing hands and physical distancing are core components of containment efforts to 'flatten-the-curve'. Development of a coronavirus vaccine is progressing at unprecedented speed but is still at least 12-18 months away. In the meantime, there is hope that a long ago discovered antimalarial drug, hydroxychloroquine, may have life-saving therapeutic efficacy against COVID-19. And if it does, we hope that this simple QTc surveillance strategy, enabled by innovation and FDA's emergency approval, will help prevent altogether or at least

significantly reduce the number of drug-induced ventricular arrhythmias and sudden cardiac deaths, particularly if there becomes wide-spread adoption and utilization of these medications for COVID-19.

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FIGURE LEGENDS

Figure 1 | Approach to mitigating the risk of DI-TdP/DI-SCD in COVID-19 patients treated following a hypothetical treatment algorithm with "off label" hydroxychloroquine alone or in combination with azithromycin. Both medications are known hERG-blockers with both QTc prolonging and torsadogenic potential. The estimated 99th percentile QTc values, derived from otherwise healthy individuals, which places a patient in the "Green Light" category are < 460 ms before puberty, < 470 ms in men, and < 480 ms in women. We estimate that the baseline QTc assessment will place 90% in "Green Light", 9% in "Yellow Light", and 1% in "Red Light" status. [*]Severe COVID-19 cases defined as a RR ≥ 30 (adults) or 40 (children), oxygen saturation ≤ 93%, PaO_2/FiO_2 ratio < 300, or lung infiltrates involving >50% of the lung field after 24-48 hours. [#]Hydroxychloroquine inhibits SARS-CoV-2 *in vitro* and reduces viral burden in a small French study. No randomized control trial data is available to support the clinical efficacy of hydroxychloroquine use in COVID-19 and its use remains "off label" presently. [¥]Re-purposed antiviral alternatives such as lopinavir/ritonavir also have QTc-prolonging effects. Abbreviations: BID, twice daily; CKD, chronic kidney disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 19; CV, cardiovascular DI-TdP, drug-induced torsades de pointes; DI-SCD, drug-induced sudden cardiac death; IV, intravenous; NIAID, National Institute of Allergy and Infectious Disease; PO, by mouth; and QTc, heart rate-corrected QT interval.

Figure 2 | Protocols for the possible inpatient and outpatient use of a smartphone-enabled mobile ECG to assess and monitor QTc values in COVID-19 patients. a) Inpatient protocol using dedicated institutional smartphone/tablet and mobile ECG device. Whenever possible, we recommend strongly the use of a dedicated institutional Bluetooth-enabled smartphone or tablet device that is not used for personal use (i.e. phone calls or other activities) to limit the spread of SARS-CoV-2. b) Inpatient or outpatient protocol using personal (or institutionally loaned) smartphone/tablet and mobile ECG device. *Currently, the only smartphone-enabled mobile ECG with FDA approval for QTc monitoring is the AliveCor KardiaMobile-6L device. Abbreviations: COVID-19, coronavirus disease 19; ECG, electrocardiogram; FDA, Food and Drug Administration; PPE, personal protective equipment; and QTc, heart rate-corrected QT interval.

TABLES

Table 1 | Torsadogenic Potential and Post-Marketing Adverse Events Associated with Possible COVID-19 Re-Purposed Pharmacotherapies

Possible COVID-19 Therapy	*In Vitro* Inhibition of SARS-CoV-2	CredibleMeds Classification	VT/VF/TdP/ LQTS in FAERS[#]	Cardiac Arrest in FAERS [#]	Refs.
Re-purposed antimalarial agents					
Chloroquine	Yes	Known TdP Risk	72	54	[3, 18, 19]
Hydroxychloroquine	Yes	Known TdP Risk	222	105	[4, 20]
Re-purposed antiviral agents					
Lopinavir/ritonavir	Unknown[*]	Possible TdP Risk	27	48	[21-23]
Adjunct agents					
Azithromycin	Unknown	Known TdP Risk	396	251	[24, 25]

[#]Adverse event reporting from post-marketing surveillance does not account for prescription volume and is often subjected to significant bias from confounding variables, quality of reported data, duplication, and underreporting of events.

*****Lopinavir/ritonavir has been shown to inhibit other SARS viruses *in vitro*. However, a recent randomized trial demonstrated no benefit in COVID-19.

Abbreviations: COVID-19, coronavirus disease 2019; FAERS, Food and Drug Administration Adverse Event Reporting System; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus; and TdP, torsades de pointes

Table 2 | Modifiable and Non-Modifiable Risk Factors for Drug-Induced Long QT Syndrome/Torsades de Pointes*
Modifiable Risk Factors
Electrolyte disturbances
Hypocalcemia (< 4.65 mg/dL)
Hypokalemia (< 3.4 mmol/L)
Hypomagnesemia (< 1.7 mg/dL)
QT-prolonging medication polypharmacy
Concurrent use of ≥ 1 medication from www.crediblemeds.com
Non-Modifiable Risk Factors
Common Diagnoses
Acute coronary syndrome
Anorexia nervosa or starvation
Bradyarrhythmias < 45 bpm
Cardiac heart failure (Ejection Fraction < 40%; uncompensated)
Congenital long QT syndrome or other genetic susceptibility
Chronic renal failure requiring dialysis
Diabetes mellitus (Type 1 and 2)
Hypertrophic cardiomyopathy
Hypoglycemia (documented and in the absence of diabetes)
Pheochromocytoma
Status post cardiac arrest (within 24 hours)
Status post syncope or seizure (within 24 hours)
Stroke, subarachnoid hemorrhage, or other head trauma (within 7 days)
Clinical History
Personal or family history of QT interval prolongation or sudden unexplained death in the absence of a clinical or genetic diagnosis
Demographic
Elderly (> 65 years of age)
Female gender
*A "pro-QTc" score ≥ 4 based on risk factors similar to those listed above was an independent predictor of mortality in patients with QT interval prolongation.[9] Unfortunately, the predictive value of these risk factors in patients with normal or borderline QT intervals has not been assessed. Adapted from Giudicessi et al[26] with permission. Copyright © 2018, Wiley.

Figure 1

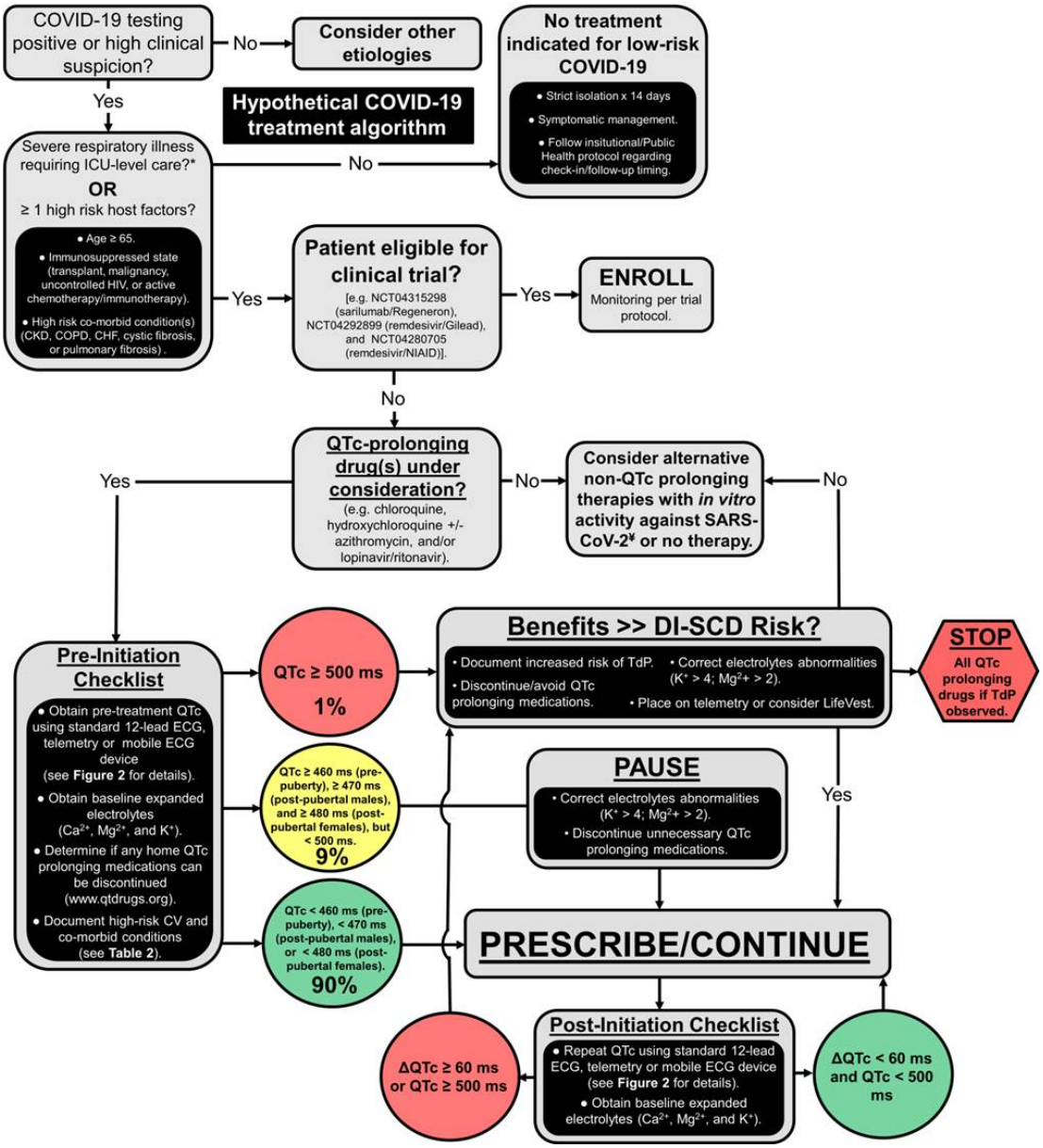

Figure 2