Canadian Heart Rhythm Society
Société canadienne de rythmologie

# Guidance on Minimizing Risk of Drug-Induced Ventricular Arrhythmia During Treatment of COVID-19: A Statement from the Canadian Heart Rhythm Society

***The COVID-19 pandemic is causing wide-spread illness and has no proven therapies. Some proposed treatments may lead to drug-induced proarrhythmia. This Canadian Heart Rhythm Society position statement proposes risk minimization strategies to identify those at highest risk while minimizing unnecessary testing, which may increase exposure of other patients and caregivers to infectious risk***.

*The Canadian Heart Rhythm Society is an Affiliate organization of the Canadian Cardiovascular Society.*

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## Abstract

The COVID-19 pandemic has led to efforts at rapid investigation and application of drugs which may improve prognosis, but for which safety and efficacy are not yet established. This document attempts to provide reasonable guidance for use of antimicrobials which have uncertain benefit but may increase risk of QT prolongation and ventricular proarrhythmia, notably, chloroquine, hydroxychloroquine, azithromycin, and lopinavir/ritonavir. During the pandemic, efforts to reduce spread and minimize effects on health care resources mandate minimization of unnecessary medical procedures and testing.

We recommend that the risk of drug proarrhythmia be minimized by:

1. discontinuing unnecessary medications which may also increase the QT interval,
2. identifying outpatients who are likely at low risk and do not need further testing (no history of prolonged QT, unexplained syncope or family history of premature sudden cardiac death, no medications which may prolong the QT interval, and/or prior known normal QTc), and
3. performing baseline testing in hospitalized patients or those who may be at higher risk. If baseline ECG testing reveals a moderately prolonged QTc, optimization of medications and electrolytes may permit therapy. If the QTc is markedly prolonged, drugs which further prolong it should be avoided, or expert consultation may permit administration with mitigating precautions.

These recommendations are made while there are no known effective treatments for COVID-19 and should be revisited when further data on efficacy and safety becomes available.

## Background

The emergence of COVID-19 has prompted rapid investigation of potential therapeutic options. Some early candidates have included chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir, remdesivir, ribavirin and others.[1] Some of these are known to pose a risk of ventricular arrhythmia. With an uncertain degree of potential for benefit, an assessment of risk of therapy should be undertaken. During the pandemic, avoidance of non-essential testing, including ECG, reduces exposure of health care workers and other patients to infectious risk, and is recommended when possible.[2] It should be noted that the advice included here is offered during a health care crisis when access to some medical tests may increase population infection risk, the potential for benefit of these drugs is unknown, and there are no treatments with clear efficacy beyond supportive care. These recommendations should be reevaluated when these factors change.

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| **Chloroquine and hydroxychloroquine** | The current data supporting the use of chloroquine or hydroxychloroquine for treatment of infection with SARS-CoV-2 includes evidence of *in vitro* activity against SARS-CoV-2,[3-5] and limited evidence from non-comparative clinical research.[6, 7]<br><br>Clinical trial results from China[6] have not yet been published in peer-reviewed form at time of writing, and data from France[7] are useful, but are preliminary. The study was nonrandomized and the preliminary report included only viral RNA detection from nasopharyngeal swabs as its primary endpoint, rather than clinical outcomes. Although limited, the data has been sufficient to prompt recommendations for treatment from national agencies in China and Italy.[8, 9]<br><br>The overall safety of these drugs has been established over several decades of use, with good cardiovascular safety profiles in small studies.[10] However, cases of QT prolongation and torsade de pointes (TdP) have been reported.[11, 12] Larger cohort studies have focused on the low risk of retinopathy associated with chronic administration.[13] Rare cases of cardiomyopathy, AV block and bundle branch block have been reported during both acute and chronic administration. |
| **Azithromycin** | Azithromycin has been suggested to have in vitro antiviral activity against other viruses,[14, 15] and is effective in treating bacterial pneumonia.<br><br>In the French series,[7] 6 patients were treated with azithromycin in addition to hydroxychloroquine, and had further reductions in detectable viral load.<br><br>Azithromycin is known to have increased risk of QT prolongation[16],TdP and sudden cardiac death (SCD)[17] however, the absolute risk is small[17] and it has been shown to be used safely in clinical practice without routine ECG-based QT interval surveillance.[18] |
| **Lopinavir/ritonavir** | Lopinavir is a protease inhibitor developed to treat HIV infection, often combined with ritonavir, which prolongs its plasma half-life, and was shown to have in vitro, as well as clinical activity against SARS-CoV[19, 20] and in vitro activity against MERS-CoV.[21]<br><br>It has been evaluted in small observational series[22-24] and has been tested in a prospective randomized controlled trial against COVID-19 for patients with radiographic evidence of pneumonia and impaired oxygen exchange, in which it did not demonstrate a measurable improvement in clinical course.[25] |
| **Combinations of drugs** | Data regarding combinations of drugs used to treat COVID-19 are insufficient to draw reliable conclusions about the safety of this approach.<br><br>It is important to note that combining more than one proarrhythmic medication is known to increase the risk of significant QT prolongation[26] however, the risk of medication-induced TdP is quite variable with an incidence that ranges between 0.001% to 8%; depending on medication used.[27] |
| **Other candidate drugs** | Other drugs which are being investigated for activity to treat COVID-19 include remdesivir, favipiravir, ribavirin, sarilumab, and baricitinib and have limited data available regarding effects on cardiac arrhythmias.[28] |

## Patients with higher clinical risk

Some patients may be at elevated clinical risk for drug-induced ventricular arrhythmia. Patients with inherited long QT syndrome are known to be at increased risk. Expert opinion may be helpful in determining how best to mitigate risk for patients with prolonged baseline QTc interval who have COVID-19.[29] The use of other drugs or medical conditions that may prolong the QT interval or otherwise interact with these medications may increase risk of adverse events. Drug-induced prolongation of the QT interval in vulnerable patients may be exacerbated in older patients, by coexistent cardiac conditions such as cardiomyopathy, ischemia, heart failure, or bradycardia, and by other conditions such as diabetes, electrolyte abnormalities, hypoglycemia or renal failure. It is possible that severe cases of COVID-19 would be more vulnerable to QT prolongation as well. It is likely that patients at higher clinical risk of drug-induced arrhythmia will also be at higher risk for more severe infectious complications and are more likely to be treated as in-patients, in which case ECG monitoring will more likely be indicated for supportive medical care. This is reflected in the recommendations below.

## Putting arrhythmic risk in context

The anticipated risk of life-threatening arrhythmia from the medications included here is likely to be low; the potential for benefit remains uncertain. Methods to mitigate risk are warranted, but should not impose undue increased risk of infection to other patients, health care workers, or place undue increase in demand on medical resources during a time of crisis with potential restrictions on access to personal protective equipment, drug therapy and even care providers.[2]

If COVID-19 antimicrobial drugs reduce mortality rate by even 5%, it is likely that this would constitute a substantial net benefit in comparison to the risk of drug-induced sudden death, recognizing that the absolute levels of risk and benefit are unclear at present. Clinical risk scores may be useful in minimizing risk,[26] but ultimately the decision whether to require extra testing and monitoring will require balancing of potential individual benefit against the risk of individual and population harm. This includes the local prevalence of COVID-19 infection and associated risk of subjecting patients to important albeit discretionary testing such as an ECG. It is recognized that assessment of the balance of risks may differ in different jurisdictions.[30]

## Alternative testing methods

Single-use or easily sterilized hand-held cardiac rhythm monitoring devices have become increasingly available and may permit reliable recording of cardiac intervals. Availability of means to perform these recordings may obviate the need for obtaining a standard 12-lead ECG and may not pose an infectious risk. If available, this may be utilized to confirm a patient's risk status prior to initiation of antimicrobial therapy, and may reduce personal risk without a meaningful increase in concomitant population risk.[31, 32]

## Recommendations

The use of medications with unproven benefit for treatment of COVID-19 should primarily focus on robust evaluation within a clinical trial whenever possible. We recommend that clinical trials include an effort to mitigate the risk of treating patients with a known predictably high risk of torsade de pointes with drugs which may further prolong the QT interval.
If drugs with the potential to cause ventricular arrhythmia through prolongation of repolarization, including azithromycin, chloroquine, hydroxychloroquine, lopinavir/ritonavir are contemplated for treatment of COVID-19, the following precautions should be observed:

1. Review medications and discontinue unnecessary medications that may prolong QT.[28]
2. For patients with known inherited long QT syndrome or a history of drug-induced torsade de Pointes, use of these drugs should be undertaken only after consultation with a heart rhythm specialist. Potential mitigations could include use of cardiac monitoring, or repeated QTc interval checks. Risk and potential benefit should be individually assessed.
3. For patients with no history of prolonged QT, unexplained syncope or family history of premature sudden cardiac death, who are not taking other medications which may prolong the QT interval, and for patients with a prior known normal QTc, it may be reasonable to proceed with antimicrobial drug administration without a baseline or follow-up ECG, if obtaining an ECG may increase population risk of infection.
4. For hospitalized patients, or for those not fulfilling the above criteria
    a) Obtain baseline assessment of:
        i. ECG to assess QTc if not performed within last 3 months
        ii. electrolytes ($Ca^{++}$, $Mg^{++}$, $K^{+}$) if possible
    b) If QTc ≥ 500 ms, reassess after correction of electrolyte abnormalities or discontinuation of other QT prolonging drugs. If QTc remains ≥ 500 ms, recommend expert consultation and careful evaluation of benefits and risks.
    c) If QTc is ≥470 ms (male) or QTc is ≥480 ms (female), but < 500 ms, initiate antimicrobial drugs and consider repeat ECG in 48 hours.
    d) If patients have clinically severe disease, or are taking multiple medications which may prolong QT, recheck QTc 48 hours after initiation of antimicrobial drugs.
    e) If follow-up QTc increases by ≥ 60 ms OR is ≥ 500 ms, discontinue antimicrobial or seek expert consultation.

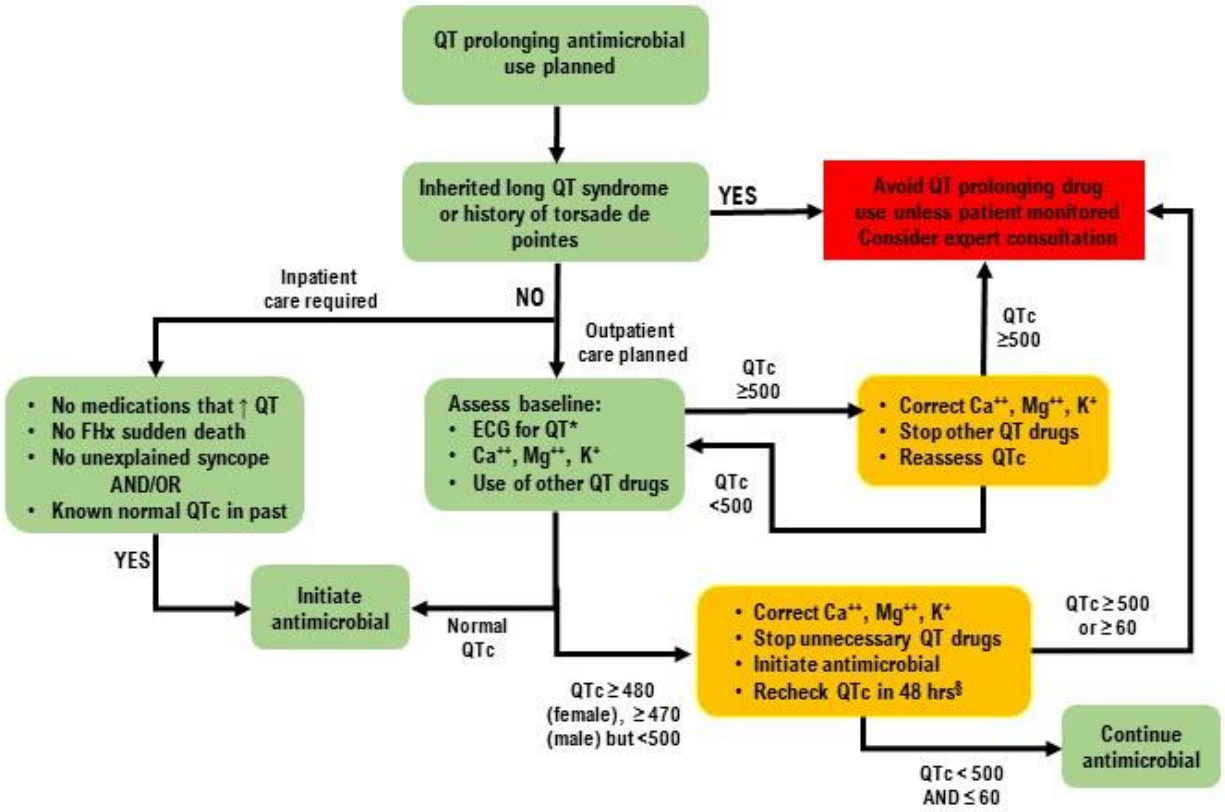


**Figure 1: Treatment algorithm for COVID-19 therapies which may prolong QT.** We recommend that use of these drugs for treating COVID-19 be within evaluative clinical trials. Note that this approach applies during a pandemic and may differ when the population risk of routine testing changes.
*See figure 2 for a review of how to measure the QT interval and calculate QTc.
§ Consider rechecking the QTc interval at 48 hours for inpatients with high risk features (see text) or in those with borderline QTc prolongation at baseline.

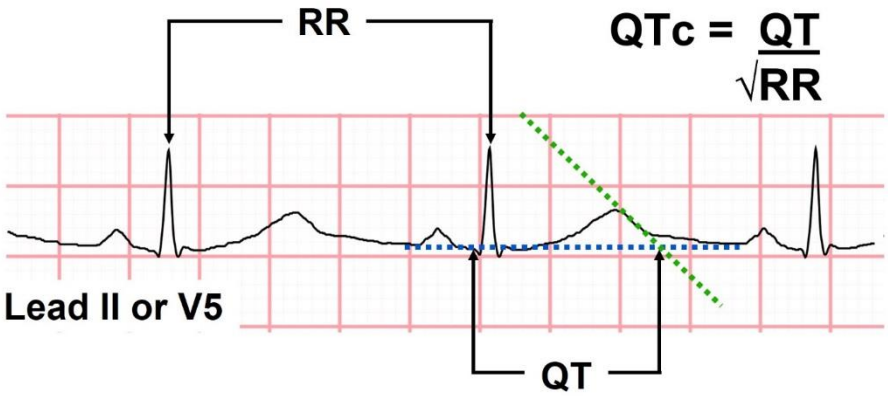


**Figure 2: How to measure the corrected QT (QTc) interval.** The QT interval is measured from the onset of the QRS (where it first deviates from baseline) to the intersection of the tangent of the downslope (dotted green line) with the baseline (TP segment, dotted blue line). This is corrected for heart rate by dividing by the square root of the RR interval, measured in seconds. In the presence of QRS widening (e.g. bundle branch block or paced ventricular rhythm) the QTc can be adjusted by subtracting the QRS duration (QRSd) which is in excess of 100 ms as in the following formula:[31,33]

$$QTc(adjusted) = QTc(measured) - (QRSd - 100)$$

If the patient is in atrial fibrillation, the QTc interval can be determined from 10-averaged AF beats.[34]

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