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Guidance on Minimizing Risk of Drug-Induced Ventricular Arrhythmia During Treatment of COVID-19: A Statement from the Canadian Heart Rhythm 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 the use of antimicrobials which have uncertain benefit but may increase risk of QT interval 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 that may also increase the QT interval, 2) identifying outpatients who are likely to be at low risk and do not need further testing (no history of prolonged QT interval, unexplained syncope, or family history of premature sudden cardiac

RÉSUMÉ

La pandémie de COVID-19 a donné lieu à des initiatives visant à accélérer l'étude et l'utilisation de médicaments susceptibles d'améliorer le pronostic des patients, mais dont l'innocuité et l'efficacité n'ont pas encore été établies. Les auteurs tentent de formuler des lignes directrices raisonnables quant à l'emploi d'agents antimicrobiens, notamment la chloroquine, l'hydroxychloroquine, l'azithromycine et l'association lopinavir-ritonavir, dont les bienfaits demeurent incertains, mais qui sont susceptibles d'accroître le risque d'allongement de l'intervalle QT et de proarythmie ventriculaire. Durant la pandémie, les efforts visant à limiter la propagation de la maladie et à atténuer au minimum les tensions exercées sur les ressources en soins de santé commandent une restriction des interventions médicales et des tests non nécessaires. Pour que le risque de proarythmie médicamenteuse demeure au plus bas, nous recommandons

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. 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 nonessential testing, including electrocardiography (ECG), reduces exposure of health care workers and other patients to infectious risk and is therefore recommended when possible.[1] An expert writing group of members of the Canadian Heart Rhythm Society was selected to derive a set of consensus-based recommendations to guide clinicians. This report was approved by the board of the Canadian Heart Rhythm Society; a fully referenced version is available as Supplementary Material.

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death, no medications that may prolong the QT interval, and/or a previous known normal corrected QT interval [QTc]), and 3) performing baseline testing in hospitalized patients or those who may be at higher risk. If baseline electrocardiographic testing reveals a moderately prolonged QTc, optimization of medications and electrolytes may permit therapy. If the QTc is markedly prolonged, drugs that 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 become available.

les mesures suivantes : 1) arrêter l'administration de médicaments non nécessaires aussi susceptibles d'allonger l'intervalle QT; 2) déterminer qui sont les patients ambulatoires présentant un risque faible et n'ayant pas besoin de subir d'autres tests (absence d'antécédents d'allongement de l'intervalle QT ou de syncope inexpliquée, d'antécédents familiaux de mort cardiaque subite prématurée ou de traitement médicamenteux susceptible d'allonger l'intervalle QT, et/ou intervalle QT corrigé [QTc] normal connu); et 3) réaliser des examens initiaux chez les patients hospitalisés ou chez ceux qui sont exposés à un risque plus élevé. Si les examens électrocardiographiques initiaux révèlent un allongement modéré de l'intervalle QTc, un traitement pourrait être administré sous réserve de l'optimisation de la médication et de l'administration d'électrolytes. Si l'allongement de l'intervalle QTc est marqué, il faut éviter d'administrer des médicaments susceptibles d'allonger davantage cet intervalle, ou encore consulter un spécialiste pour pouvoir traiter le patient en prenant les précautions qui s'imposent. Ces recommandations sont formulées à l'heure où il n'existe encore aucun traitement efficace connu contre la COVID-19; il faudra les revoir lorsque d'autres données relatives à l'efficacité et à l'innocuité des agents en cause seront disponibles.

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.

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 and limited evidence from noncomparative clinical research. Clinical trial results from China[2] had not yet been published in peer-reviewed form at the time of writing, and data from France[3] are useful but preliminary. The French study was nonrandomized, and the preliminary report included only viral RNA detection from nasopharyngeal swabs as its primary end point rather than clinical outcomes. Although limited, the data have been sufficient to prompt recommendations for treatment from national agencies in China and Italy. The overall safety of these drugs has been established over several decades of use, with good cardiovascular safety profiles in small studies. However, cases of QT interval prolongation and torsade de pointes (TdP) have been reported. Larger cohort studies have focused on the low risk of retinopathy associated with chronic administration. Rare cases of cardiomyopathy, atrioventricular 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 and is effective in treating bacterial pneumonia. In the French series,[3] 6 patients were treated with azithromycin in addition to hydroxychloroquine and had further reductions in detectable viral load. Azithromycin is known to have an increased risk of QT interval prolongation, TdP, and sudden cardiac death, but the absolute risk is small and it has been used safely in clinical practice without routine ECG-based QT interval surveillance.

Lopinavir/Ritonavir

Lopinavir is a protease inhibitor developed to treat human immunodeficiency virus 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 and *in vitro* activity against MERS-CoV. It has been evaluated in small observational series 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 the clinical course.[4]

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. It is important to note that combining more than one proarrhythmic medication is known to increase the risk of significant QT interval prolongation; however, the risk of medication-induced TdP is quite variable, with an incidence that ranges from 0.001% to 8% depending on the medications used.

Other Candidate Drugs

Other drugs that are being investigated for activity to treat COVID-19 include remdesivir, favipiravir, ribavirin, sarilumab, and baricitinib, for which limited data are available regarding effects on cardiac arrhythmias.

Patients With Higher Clinical Risk

Some patients may be at elevated clinical risk for drug-induced ventricular arrhythmia. Patients with inherited

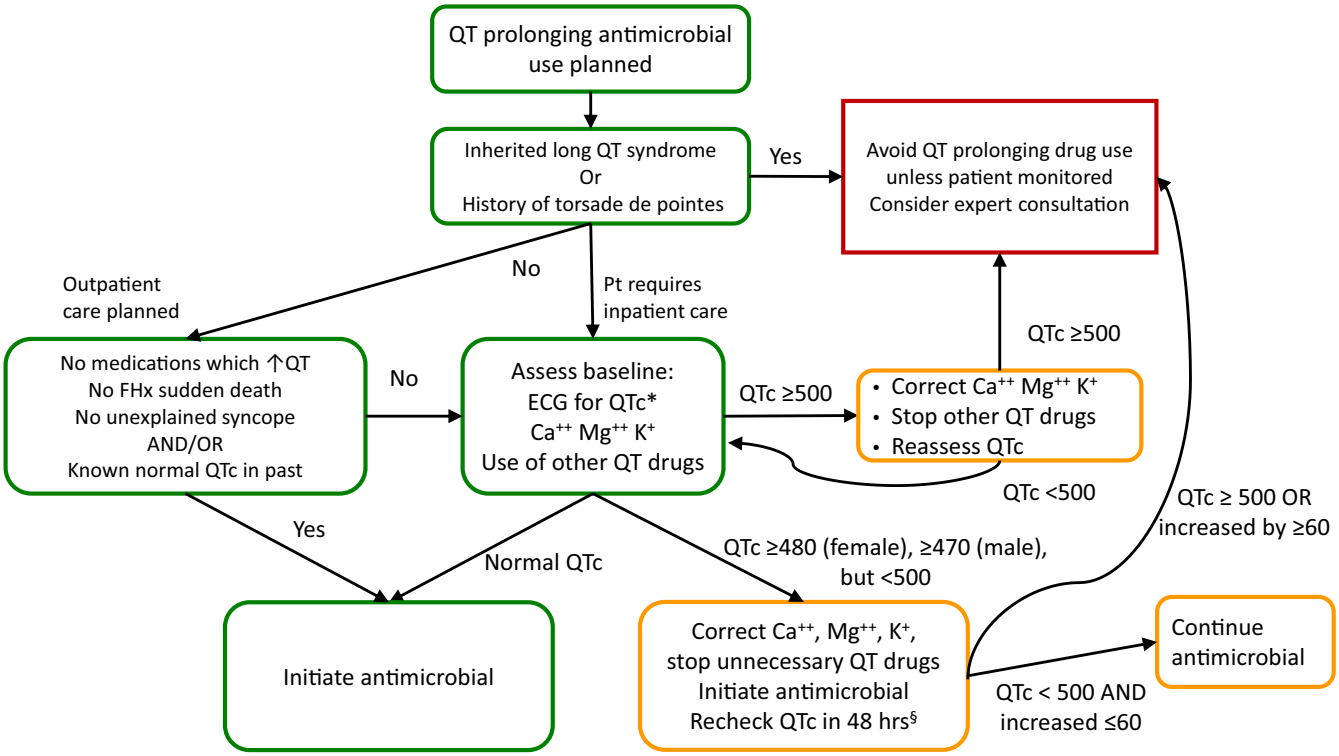

Figure 1. Treatment algorithm for COVID-19 therapies that may prolong QT interval. We recommend that the use of these drugs for treating COVID-19 be within evaluative clinical trials. Note that this approach applies during a pandemic and may differ when the population risk of routine testing changes. *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 those with borderline QTc prolongation at baseline. ECG, electrocardiography; QTc, corrected QT interval.

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 corrected QT interval (QTc) who have COVID-19. 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 interval prolongation as well. It is likely that patients at higher clinical risk of drug-induced arrhythmia would also be at higher risk for more severe infectious complications and are more likely to be treated as inpatients, in which case ECG monitoring would more likely be indicated for supportive medical care. This is reflected in the recommendations below.

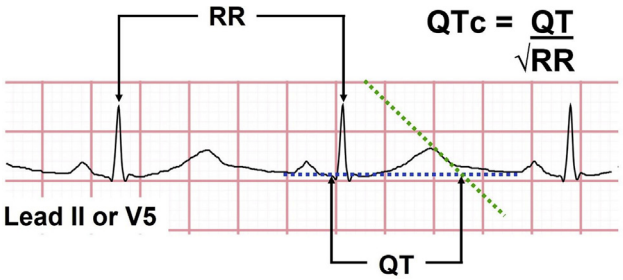

Figure 2. How to measure the corrected QT interval (QTc). The QT interval is measured from the onset of the QRS (where it first deviates from baseline) to the intersection of the tangent of the downslope (**dotted green line**) with the baseline (TP segment, **dotted blue line**). This is corrected for heart rate by dividing by the square root of the RR interval, measured in seconds. In the presence of QRS widening (eg, bundle branch block or paced ventricular rhythm), QTc can be adjusted by subtracting the QRS duration (QRSd) that is in excess of 100 ms as in the following formula: QTc(adjusted) = QTc(measured) − (QRSd − 100). If the patient is in atrial fibrillation, the QTc interval can be determined from 10 averaged atrial fibrillation beats.

Putting Arrhythmic Risk in Context

The anticipated risk of life-threatening arrhythmia from the medications included here is likely to be low, while the potential for benefit remains uncertain. Methods to mitigate risk are warranted, but should not impose undue increased risk of infection to other patients or health care workers, or 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.[1] If COVID-19 antimicrobial drugs reduce mortality rate by even 5%, it is likely that this would constitute a substantial net benefit compared with 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, 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 ECG. It is recognized that assessment of the balance of risks may differ in different jurisdictions.

Alternate 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 such 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, they may be used to confirm a patient's risk status before initiation of antimicrobial therapy and may reduce personal risk without a meaningful increase in concomitant population risk.

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 TdP with drugs that may further prolong the QT interval.

If drugs with the potential to cause ventricular arrhythmia through prolongation of repolarization, including azithromycin, chloroquine, hydroxychloroquine, and lopinavir/ritonavir, are contemplated for treatment of COVID-19, the following precautions should be observed (see Fig. 1):

- Review medications and discontinue unnecessary medications that may prolong the QT interval.[5]
- For patients with known inherited long QT syndrome or a history of drug-induced TdP, 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 checks. Risk and potential benefit should be individually assessed.
- For patients with no history of prolonged QT interval, unexplained syncope, or family history of premature sudden cardiac death and who are not taking other medications that may prolong the QT interval, as well as patients with a previous 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.
- For hospitalized patients, or for those not fulfilling the above criteria:
  - Obtain baseline assessment of:
    - ECG to assess QTc if not performed within the past 3 months (see Fig. 2).
    - Electrolytes (Ca^{++}, Mg^{++}, K^{+}) if possible.
  - If QTc $\geq$ 500 ms, reassess after correction of electrolyte abnormalities or discontinuation of other QT interval–prolonging drugs. If QTc remains $\geq$ 500 ms, seek expert consultation and carefully evaluate benefits and risks.
  - If QTc is $\geq$ 470 ms (male) or QTc is $\geq$ 480 ms (female), but $<$ 500 ms, initiate antimicrobial drugs and consider repeated ECG in 48 hours.
  - If patients have clinically severe disease or are taking multiple medications that may prolong QT, recheck QTc 48 hours after initiation of antimicrobial drugs.
  - If follow-up QTc increases by $\geq$ 60 ms or is $\geq$ 500 ms, discontinue the antimicrobial drugs or seek expert consultation.

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 become available.

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Supplementary Material

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