

Prevention of Ventricular Arrhythmia and Sudden Cardiac Death in COVID-19 Patients

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ABSTRAK

Sejak kasus pertama dilaporkan pada akhir 2019, COVID-19 telah menyebar ke seluruh dunia dan menjadi pandemi. Tingginya tingkat penularan virus, menjadi ancaman bagi kesehatan masyarakat secara global. Infeksi virus dapat memicu sindrom koroner akut, aritmia, dan timbulnya eksaserbasi gagal jantung. Hal ini terutama diakibatkan kombinasi respon inflamasi sistemik yang signifikan disertai inflamasi vaskular terlokalisir pada plak arteri, bersama dengan efek lainnya. Panduan praktik klinis di Indonesia untuk tata laksana COVID-19 menyebutkan bahwa hydroxychloroquine sendiri atau kombinasi dengan azithromycin berpotensi digunakan untuk terapi COVID-19. Namun, chloroquine, hydroxychloroquine, dan azithromycin dapat memperpanjang interval QT. Hal ini meningkatkan kekhawatiran tentang risiko kematian akibat aritmia dari penggunaan obat ini secara individu atau kombinasi. Sampai saat ini masih belum ada vaksin dan antivirus spesifik untuk terapi COVID-19, sehingga pencegahan untuk pada pasien dengan risiko kardiovaskular dan efek samping pengobatan sangat diperlukan.

Kata kunci: COVID-19, aritmia, hydroxychloroquine, azithromycin, pemanjangan interval QT.

ABSTRACT

Since the first case was reported at the end of 2019, COVID-19 has spread throughout the world and has become a pandemic. The high transmission rate of the virus has made it a threat to public health globally. Viral infections may trigger acute coronary syndromes, arrhythmias, and exacerbation of heart failure, due to a combination of effects including significant systemic inflammatory responses and localized vascular inflammation at the arterial plaque level. Indonesian clinical practice guideline stated that (hydroxy)chloroquine alone or in combination with azithromycin may be used to treat for COVID-19. However, chloroquine, hydroxychloroquine, and azithromycin all prolong the QT interval, raising concerns about the risk of arrhythmic death from individual or concurrent use of these medications. To date, there is still no vaccine or specific antiviral treatment for COVID-19. Therefore, prevention of infection in people with cardiovascular risk and mitigation of the adverse effects of treatment is necessary.

Keywords: COVID-19, arrhythmia, hydroxychloroquine, azithromycin, prolong QT interval.

INTRODUCTION

COVID-19 has reached a pandemic level and is a threat to global health. Its course is still evolving. Lessons from the previous coronavirus and influenza epidemics suggest that viral infections can trigger acute coronary syndromes, arrhythmias, and exacerbation of heart failure, due to a combination of effects including significant systemic inflammatory responses and localized vascular inflammation at the arterial plaque level.¹

Patients with pre-existing cardiovascular disease may have a worse prognosis than others, although age could be one of the confounders. Furthermore, although most clinical presentations involve the respiratory system, the disease may also impact on the cardiovascular system. Angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor for coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV2, the causative virus of COVID-19. Besides its expression in the respiratory system, ACE2 is found in the human cardiovascular system including the heart. Infection by SARS-CoV2 can cause damage to the myocardium, although the specific mechanisms are uncertain.²

Pro-arrhythmic effects of COVID-19-related issues include fever, stress, electrolyte disturbances, and pharmacological treatment. These may impact patients with an increased risk for cardiac arrhythmias, either secondary to acquired conditions, as comorbidities, or consequent to inherited syndromes. The safety of QT-prolonging medications may be maximized by close monitoring and optimization of these factors.^{1,2}

LONG QT SYNDROME

A registry of 1099 cases with COVID-19 reported a higher prevalence of hypertension and coronary artery disease in severely affected versus non-severely affected patients. Another study compared patients admitted to the intensive care unit (ICU) and on-ICU patients. Higher rates of hypertension and cardiovascular diseases were observed in ICU patients.^{3,4}

COVID-19 may have an arrhythmogenic effect, potentially contributing to disease

outcome—this could be of importance for patients with an increased risk for cardiac arrhythmias, either secondary to acquired conditions, comorbidities, or consequent to inherited syndromes. Inherited arrhythmia syndromes such as long QT syndrome (LQTS), Brugada syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (VT) in the setting of the COVID-19 pandemic may prove particularly challenging. These patients may be susceptible to the pro-arrhythmic effects of COVID-19-related issues such as fever, stress, electrolyte disturbances, and the use of antiviral drugs. Hence, additional precautions and preventive measures are recommended, including electrocardiogram (ECG) monitoring, aggressive antipyretic treatment, and more stringent social distancing to prevent infection.^{5,6}

LQTS is characterized by abnormally prolonged ventricular repolarization and an increased risk of the malignant arrhythmia torsades de pointes and ventricular fibrillation that may lead to sudden death. The greatest risk factor for malignant arrhythmias in patients with LQTS or acquired QT prolongation is the use of one or more corrected QT interval (QTc)-prolonging drugs in the setting of severe manifestation of COVID 19.⁶ COVID-19 treatment with a combination of (hydroxy) chloroquine and additional antivirals, or with azithromycin, may result in higher plasma levels and significant QT prolongation. Physicians should also be aware of the alpha-blocking effects of (hydroxy)chloroquine, which might result in hypotension.⁶

The patient's baseline QTc value should be obtained before administering any drugs with the potential to prolong the QT interval. There is still no guidance regarding how to monitor outpatients that use (hydroxy)chloroquine. Ambulatory ECG monitoring may be considered. It is also important for patients being treated with QT-prolonging drugs to report promptly any new symptoms including palpitation, syncope, or near syncope. They should also report clinical changes that could lead to hypokalemia, such as gastroenteritis or the initiation of diuretic therapy.^{6,7}

In general, patients with the following QTc intervals are at low risk for significant QT prolongation and polymorphic VT:

- QTc < 460 ms in pubertal males/females
- QTc < 470 ms in postpubertal males
- QTc < 480 ms in postpubertal females.

PREVENTION OF ARRHYTHMIA AND SUDDEN CARDIAC DEATH IN LQTS PATIENTS

Patients with the baseline QTc interval ≥ 500 ms (with a QRS ≤ 120 ms) are at increased risk for significant QT prolongation and polymorphic VT.⁸ In such patients, efforts should be made to correct any contributing electrolyte abnormalities: for hypokalemia correct to a level of > 4 mEq/l and for hypomagnesemia correct to a level of > 2 mg/dl. Withhold the drugs in patients with baseline QT interval prolongation (QTc 500 ms) or with known congenital LQTS.⁷ Patients with a risk of QT prolongation or history of LQTS that are hospitalized with COVID-19 infection need monitoring, dose adjustment, and possibly drug discontinuation.⁷

Patients must be monitored and serum potassium optimized daily. An ECG should be acquired 2-3 h after the second dose of (hydroxy)chloroquine, and daily thereafter. If QTc increases by > 60 ms and/or absolute QTc > 500 ms (or > 530 – 550 ms if QRS > 120 ms), azithromycin should be discontinued and/or the dose of (hydroxy)chloroquine should be reduced, and the ECG should be repeated daily. If the QTc remains increased, the risk and benefit of ongoing therapy should be re-evaluated, consultation with an electrophysiologist should be considered, and discontinuation of (hydroxy)chloroquine should also be considered. There should be a reevaluation of the risk of torsades de pointes versus benefit of the medication, with the considerations as follows:⁸

- Recognition that there is an increased risk of torsades de pointes,
- Discontinuation of all other QT-prolonging medications,
- Correction of all electrolyte abnormalities,
- Placement of the patient in continuous telemetry, with consideration of a wearable defibrillator or placement of external defibrillator patches,

- Discontinuation of (hydroxy)chloroquine, azithromycin, or other medication if torsades de pointes develops.

The safety of QT-prolonging medications may be maximized by close monitoring and optimization of these factors. A risk score has been derived and validated by Tisdale et al., for prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients (Table 1 and 2).⁹

Table 1. Risk score for drug-associated QTc prolongation

Risk Factors	Points
Age ≥ 68 y	1
Female sex	1
Loop diuretic	1
Serum K ⁺ ≤ 3.5 mEq/l	2
Admission QTc ≥ 450 ms	2
Acute MI	2
≥ 2 QTc-prolonging drugs	3
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Maximum risk score	21

QTc, corrected QT interval; MI, myocardial infarct. Risk scores as derived and validated by Tisdale et al.⁹

Table 2. Risk levels for drug-associated QT prolongation

Risk Levels	Points
Low Risk	≤ 6
Moderate Risk	7–10
High Risk	≥ 11

This scoring can help clinicians to monitor COVID-19 patients given (hydroxy)chloroquine and azithromycin so that mortality and morbidity caused by these combinations can be reduced. However, there are still no data showing that this scoring can help prevent drug-associated torsades de pointes.⁹

Patients admitted with COVID-19 are likely to have longer baseline QTc and have higher potential arrhythmic risks as a result of the metabolic and physiologic sequelae of their illness, and typically a greater burden of comorbid disease. The goal of QTc screening in this setting is not to identify patients who

are not candidates for therapy but to identify those who are at increased risk for torsades de pointes, so aggressive countermeasures may be implemented.⁸ The QTc calculation for screening can use several formulas, which are summarized in **Table 3**.

Table 3. QTc formulas.

QTc formulas	Equation
Fridericia	$QTc = QT / \sqrt[3]{RR}$
Framingham	$QTc = QT + 0.154(1-RR)$
Hodges	$QTc = QT \cdot 1.75(HR-60)$
Bazett	$QTc = QT / \sqrt{RR}$

Fridericia or Framingham correction should be considered especially for heart rates > 90 bpm¹⁰

Patients who are stable for outpatient therapy may be less at risk for complications, but are unlikely to have access to close monitoring. If ECG assessment of an outpatient is impossible or poses an undue risk of infection for others, the necessity of treatment should be balanced against

risk when considering alternative monitoring methods or omitting monitoring. If quarantine or resource constraints are prohibitive, consider performing no further ECG/telemetry assessment if the Tisdale risk score ≤ 6 . Otherwise, ECG should be repeated 2-3 h after dosing on day 3 of therapy. If QTc increases by > 30–60 ms or absolute QTc > 500 ms (or > 530–550 ms if QRS > 120 ms), discontinuing therapy should be considered.^{7,8} The drug administration flowchart based on QT is shown in **Figure 1**.

BRUGADA SYNDROME

Brugada syndrome is a familial arrhythmia syndrome disorder characterized by the type 1 Brugada ECG pattern in the right precordial leads of the ECG and an increased risk for ventricular fibrillation and sudden cardiac death. The most frequently-used drugs for COVID-19 patients are not on the list of drugs to be avoided by Brugada syndrome patients.^{6,11}

However, attention to Brugada syndrome

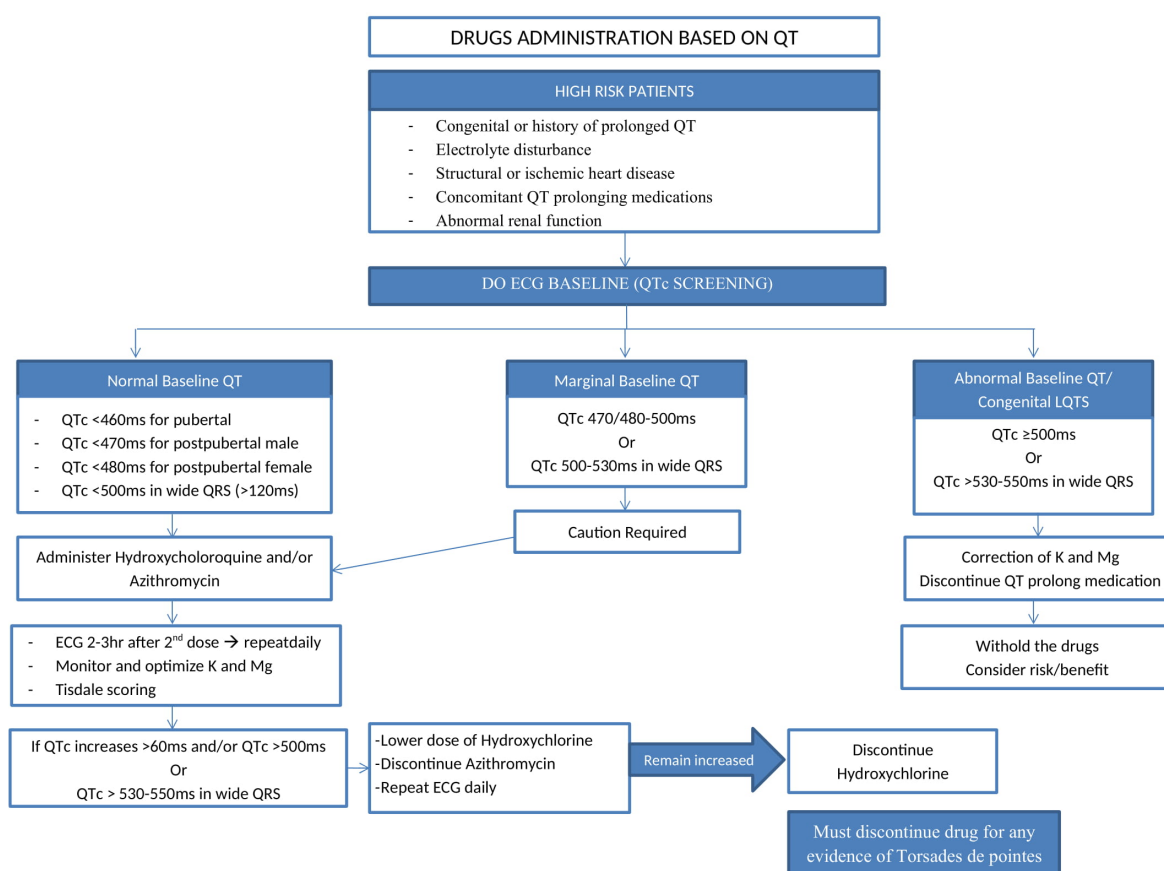


Figure 1. The drug administration flowchart based on QT.

management is relevant in the setting of the COVID-19 outbreak since ECG manifestations of the disorder may be uncovered during fever, and since fever has been unequivocally associated with life-threatening arrhythmic events in patients with the disorder.¹² Individuals with Brugada syndrome may be at increased risk for ventricular arrhythmias during fever. Fever may aggravate the coved-type ST-segment elevation in leads V1 and V2 that often precedes arrhythmias in Brugada syndrome.¹³

PREVENTION OF ARRHYTHMIA AND SUDDEN CARDIAC DEATH IN BRUGADA SYNDROME PATIENTS

Based on the above statement, the following recommendations are:⁶

- All patients with Brugada syndrome should self-treat with paracetamol or acetaminophen immediately if they develop signs of fever, and self-isolate.
- Patients without an implantable cardioverter defibrillator (ICD) who are at higher risk due to fever include:
 - a. Sodium channel disease with or without type 1 ECG pattern
 - b. Children and young adults (< 26 years old) and the elderly (> 70 years) with Brugada syndrome
 - c. All patients with a spontaneous type 1 Brugada pattern and/or cardiac syncope.
- If these higher-risk patients develop a high fever (> 38.5 °C) despite paracetamol treatment, they will need to attend the emergency department. Assessment should include an ECG and monitoring for arrhythmia. If an ECG shows the type 1 Brugada ECG pattern, then the patient will need to be observed until fever and/or the ECG pattern resolves. If all ECG show no sign of the type 1 ECG pattern, then they can go home to self-isolate.
- Patients who are not part of the higher-risk group and have a drug-induced type 1 ECG pattern, no symptoms of syncope, and no sign of a spontaneous type 1 pattern at any other time are at the lowest risk and can afford to self-isolate at home.

Malignant arrhythmia in the setting of elevated cardiac markers should raise suspicion of underlying myocarditis.

Although hypoxia and electrolyte abnormalities that are common in the acute phase of severe illness can potentiate cardiac arrhythmias, the exact arrhythmic risk due to COVID-19 in patients with less severe illness or those who recover from the acute phase of the severe illness is currently unknown.¹⁴ Improved understanding of this is critical, primarily in guiding decisions on whether additional arrhythmia monitoring is needed (e.g., mobile cardiac telemetry) after discharge and whether an ICD or wearable cardioverter defibrillator will be needed in those with impaired left ventricular function thought to be secondary to COVID-19.¹⁴

PROTOCOL MODIFICATIONS IN SETTINGS WITH LIMITED RESOURCES OR QUARANTINE

In settings where resource limitation or quarantines preclude the full implementation of the above guidelines, the following modifications should be used:⁸

- To minimize exposure or contact, it may be reasonable to forego ECG screening to allow patients to remain in quarantine if no high-risk features exist (history of LQTS, concomitant QT-prolonging medications, structural or ischemic heart disease, history of prolonged QTc on any ECG, history of abnormal renal function and/or electrolytes).
- All patients should have close monitoring of symptoms with attention to indicators of arrhythmia risk (syncope, dehydration, initiation of new medications, and worsening of health status).
- If telemetry resources are limited, their use must be triaged based on clinical importance. Patients already on therapy with QTc values in the acceptable range could be considered for ongoing (hydroxy)chloroquine use without telemetry. Patients initiating therapy with Tisdale risk score ≤ 6 can similarly be considered for use without monitoring. Any syncope should be considered due to polymorphic VT and should prompt to ECG and re-initiation of telemetry.

GENERAL PREVENTION

Electrocardiography

All patients in whom COVID-19 is suspected should have a baseline electrocardiogram performed at the time of entry into the health care system. Ideally, this would be a 12-lead ECG. This will allow for documenting baseline QRS-T morphology should the patient develop signs or symptoms suggestive of myocardial injury or an acute coronary syndrome. Additionally, the baseline ECG allows for documentation of the QT (and QTc) interval. Importantly, QTc will need to be monitored if QT-prolonging therapies are initiated (eg; azithromycin and chloroquine) to reduce LQTS.¹⁵

Cardiac Markers

The mortality rate has been reported to be higher in patients who had COVID-19 with high troponin T (TnT) levels than those with normal TnT levels. Patients with high TnT levels have demonstrated elevated levels of N-terminal pro B-type natriuretic peptide (NT ProBNP). Elevated NT ProBNP is related to malignant arrhythmia.¹⁶

Public Health

Clinic visits and in-person cardiac implantable electronic device checks should be changed to telehealth and remote checks whenever feasible.¹⁴ At a population level, large-scale public health interventions with preparedness plans and mitigation interventions are being developed and implemented. Public health measures include self-isolation and quarantining the infected patients as well as early detection of the disease. Aggressive compliance with basic hygiene skills along with minimizing the exposure to COVID-19 is key to preventing the spread of COVID-19 and should be strongly implemented.¹

During this pandemic, patients should avoid close contact with other patients with suspected or confirmed COVID-19 or having signs and symptoms of respiratory infection. Hand washing and social distancing are the key principles to reduce the risk of infection. Patients with underlying cardiac disease, hypertension, cardiac transplant patients, or patient taking immunosuppressive medications should take

extra precautions to avoid becoming infected.¹

CONCLUSION

Patients with pre-existing cardiovascular disease may have a worse prognosis than others, although age could be a confounding factor. These patients may be susceptible to pro-arrhythmic effects of COVID-19-related issues such as fever, stress, electrolyte disturbances and pharmacological treatment.

Treatment with (hydroxy)chloroquine and additional drugs, or with azithromycin, might result in higher plasma levels and significant QT prolongation, necessitating additional precautions and specialized management. Key precautions include hand washing and social distancing to reduce the risk of infection, aggressive antipyretic treatment to reduce fever in Brugada syndrome patients, and ECG monitoring and scoring in LQTS patients treated with antiviral drugs. Recognition of cardiovascular or arrhythmia risk in COVID-19 patients is necessary.

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