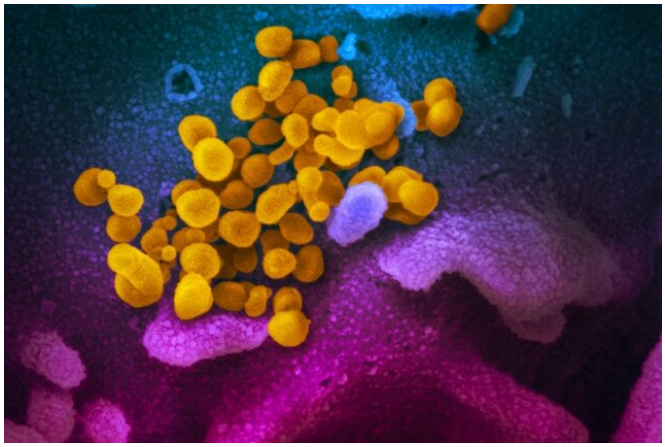
Mayo Clinic outlines approach for patients at risk of drug-induced sudden cardiac death in COVID-19

25 March 2020, by Terri Malloy



This scanning electron microscope image shows SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient, emerging from the surface of cells (blue/pink) cultured in the lab. Credit: NIAID-RML

SARS-CoV-2, the virus that causes COVID-19, continues to spread, leading to more than 20,000 deaths worldwide in less than four months. Efforts are progressing to develop a COVID-19 vaccine, but it's still likely 12 to 18 months away.

In the meantime, the pandemic, with over 400,000 confirmed cases worldwide already, is driving researchers to find safe and effective therapies for patients with COVID-19, and an antimalarial drug is potentially on the front lines of that effort. While new and repurposed drugs are being tested in clinical trials, some of these promising drugs are simultaneously being used off-label for compassionate use to treat patients.

Some of the medications being used to treat COVID-19 are known to cause drug-induced prolongation of the QTc of some people. The QTc is an indicator of the health of the heart's electrical recharging system. Patients with a dangerously prolonged QTc are at increased risk for potentially life-threatening ventricular rhythm abnormalities that can culminate in sudden cardiac death.

"Correctly identifying which patients are most susceptible to this unwanted, tragic side effect and knowing how to safely use these medications is important in neutralizing this threat," says Michael J. Ackerman, M.D., Ph.D., a Mayo Clinic genetic cardiologist. Dr. Ackerman is director of the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program.

A study published in *Mayo Clinic Proceedings* details more information about potential dangers and the application of QTc monitoring to guide treatment when using drugs that can cause heart rhythm changes. Dr. Ackerman is the senior author of the study.

Hydroxychloroquine is a long-standing preventive and treatment drug for malaria. It also is used to manage and minimize symptoms of inflammatory immune diseases, such as lupus and rheumatoid arthritis. In laboratory tests, hydroxychloroquine can prevent the SARS-CoV and SARS-CoV-2 viruses from attaching to and entering cells. If these antiviral abilities work the same way in animals and humans, the drug could be used to treat patients and limit the number of COVID-19 deaths.

On a cellular level, potential QT-prolonging medications, like hydroxychloroquine, block one of the critical potassium channels that control the heart's electrical recharging system. This interference increases the possibility that the heart's rhythm could degenerate into dangerous erratic heart beats, resulting ultimately in sudden cardiac death.

Accordingly, Mayo Clinic cardiologists and physician-scientists have provided urgent guidance on how to use a 12-lead ECG, telemetry or smartphone-enabled mobile ECG to determine the patient's QTc as a vital sign to identify those patients at increased risk and how to ultimately minimize the chance of drug-induced sudden cardiac death.

"Right now, it is the Wild West out there, ranging from doing no QTc surveillance whatsoever and just accepting this potential tragic side effect as part of 'friendly fire,' to having ECG technicians going into the room of a patient with COVID-19 daily, exposing them to coronavirus and consuming personal protective equipment," says Dr. Ackerman. "Here Mayo Clinic has stepped forward to provide timely and critical guidance."

Guidelines for QTc monitoring during treatment

The antimalarial drugs chloroquine and hydroxychloroquine, as well as the HIV drugs lopinavir and ritonavir, all carry a known or possible risk of drug-induced ventricular arrhythmias and sudden cardiac death. Prior to starting treatment with these medications, it is important to get a baseline ECG to be able to measure changes. This starting point measurement could be from a standard 12-lead ECG, telemetry or a smartphone-enabled mobile ECG device. On Monday, March 20, the Food and Drug Administration (FDA) granted emergency approval of AliveCor's Kardia 6L mobile ECG device as the only FDA-approved mobile device for QTc monitoring with COVID-19.

The mobile device's ability to remotely provide the patient's heart rhythm and QTc value does not require an extra ECG technician to take the measurement in person, thus saving increased exposure to COVID-19 and the need for more personal protective equipment.

Using the algorithm developed by Dr. Ackerman and colleagues, the potential risk of drug-induced arrhythmias can be rated and used to modify treatment accordingly. For example, patients with a baseline QTc value greater than or equal to 500 milliseconds and those that experience an acute QTc reaction with a QTc greater than or equal to 60 milliseconds from baseline after starting treatment with one or more QTc-prolonging drugs are at greatest risk for drug-induced arrhythmias. Simple QTc countermeasures can be implemented for patients with a cautionary "red light" QTc status if the decision is made to proceed with the intended COVID-19 therapies.

Information guides decisions

There are a number of considerations around the use of off-label drugs to treat COVID-19. The drugs may or may not be available in large enough supply to treat a worldwide pandemic, even at the current compassionate use stage of testing. It will take careful consideration of COVID-19 patients' circumstances for treating clinicians and patients to decide on the use of drugs or drug combinations that may treat their infection, but which potentially could cause harmful drug-induced side effects.

Dr. Ackerman says that patients under 40 with mild symptoms and a QTc greater than or equal to 500 milliseconds may choose to avoid treatment altogether, as the arrhythmia risk may far outweigh the risk of developing COVID-19-related acute respiratory distress syndrome. However, in COVID-19 patients with a QTc greater than or equal to 500 milliseconds who have progressively worsening respiratory symptoms or are at greater risk of respiratory complications due to advanced age, immunosuppression or having another high-risk condition, the potential benefit of QTc-prolonging medicines may exceed the arrhythmia risk.

"Importantly, the vast majority of patients ? about 90% ? are going to be QTc cleared with a 'green light go' and can proceed, being at extremely low risk for this side effect," says Dr. Ackerman.

Ultimately, the weighing of risks to benefits depends on whether hydroxychloroquine, with or without azithromycin, is truly an effective treatment against COVID-19.

"If it is, we hope that this simple QTc surveillance strategy, enabled by innovation and the FDA's emergency approval, will help prevent or at least significantly minimize drug-induced ventricular

arrhythmias and sudden cardiac death, particularly if the treatment is widely adopted and used to treat COVID-19," says Dr. Ackerman.

Provided by Mayo Clinic