SARS-CoV-2, COVID-19 and inherited arrhythmia syndromes

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Short title: COVID-19 and inherited arrhythmia syndromes

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Abstract

Ever since the first case was reported at the end of 2019, the SARS-COV-2 virus and associated lung disease COVID-19 has spread throughout the world and has become a pandemic. In particular, the high transmission rate of the virus has made it a threat to public health globally. Currently, there is no proven effective therapy against the virus, and the impact on other diseases is also uncertain, especially inherited arrhythmia syndrome.

Arrhythmogenic effect of COVID-19 can be expected, potentially contributing to disease outcome. This may be of importance for patients with an increased risk for cardiac arrhythmias, either secondary to acquired conditions or co-morbidities or consequent to inherited syndromes. Management of patients with inherited arrhythmia syndromes such as Long QT syndrome, Brugada syndrome, Short QT syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia in the setting of the COVID-19 pandemic may prove particularly challenging. Depending on the inherited defect involved, these patients may be susceptible to pro-arrhythmic effects of COVID-19-related issues such as fever, stress, electrolyte disturbances and use of antiviral drugs. We here describe the potential COVID-19 associated risks and therapeutic considerations for patients with distinct inherited arrhythmia syndromes and provide recommendations, pending local possibilities, for their monitoring and management during this pandemic.

Introduction

Ever since the first case was reported at the end of 2019, the SARS-COV-2 virus and associated lung disease COVID-19 has spread throughout the world and has become a pandemic. In particular, the high transmission rate of the virus has made it a threat to public health globally.[1,2] Currently, there is no proven effective therapy against the virus, and the impact on other diseases is also uncertain.

SARS-CoV-2 is an RNA virus, a member of coronavirus family of viruses, similar to SARS-CoV.[3] Like SARS-CoV, SARS-CoV-2 infects humans by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of the cell through its spike domain.[3] Infected patients present with a variety of manifestations. The most common clinical symptom is fever (88.7%). Other symptoms include cough (67.8%), shortness of breath (18.7%), myalgia or arthralgia (14.9%), headache (13.6%), diarrhea (3.8%), sore throat (13.9%), and sputum production (33.7%) and fatigue (38.1%).[4] Studies have shown that while the vast majority of patients have minor symptoms, it is also possible for infected cases to become critically ill, especially older individuals (above 60 years old) or patients with comorbidities.[1,2] Severely affected patients may have acute respiratory distress (15.6%) which requires invasive mechanical ventilation (14.5%) and extracorporeal membrane oxygenation (2.9%).[4]

Possible cardiac effects of SARS-COV-2 corona virus

A registry of 1099 cases with COVID-19 reported a higher prevalence of hypertension (23.7% vs. 13.4%) and coronary artery disease (5.8% vs. 1.8%) in severely affected versus non-severely affected patients.[4] Another study, of 138 hospitalized COVID-19 patients compared patients admitted to the intensive care unit (ICU) and non-ICU patients. Higher rates of hypertension (58.3% vs. 21.6%, p <0.001) and cardiovascular disease (25.0% vs. 10.8%, p=0.04) were observed in ICU patients.[1] This indicates that patients with pre-existing cardiovascular disease may have a worse prognosis than others although age could be one of the confounders. Furthermore, it is also essential to understand that although most clinical presentations relate to the respiratory system, the disease may also impact on the cardiovascular system.[5] Besides the respiratory system, ACE2 is expressed in the human cardiovascular system including the heart[6] and a number of mechanisms have been put forward whereby SARS-CoV-2 may cause myocardial injury. These include mechanisms involving derangement of ACE2 signal pathways (animal studies have shown that cellular ACE2 levels decrease upon SARS-CoV infection),[6] cytokine storm and myocarditis.[7,8] Occurrence of myocardial involvement and severity thereof varies among affected individuals. While myocardial damage evidenced by high cardiac markers such as hs-TnI has been recognized[9] and fulminant myocarditis has been reported,[8] whether cardiovascular complications include malignant arrhythmias is not yet known. In the afore-mentioned study of 138 hospitalized COVID-19 patients, arrhythmia (not further specified) was reported in 17%

of total patients and in 16 of 36 patients admitted to the ICU.[1] Therefore, an arrhythmogenic effect of COVID-19 could be expected, potentially contributing to disease outcome. This may be of importance for patients with an increased risk for cardiac arrhythmias, either secondary to acquired conditions, co-morbidities, or consequent to inherited syndromes. Management of patients with inherited arrhythmia syndromes such as Long QT syndrome, Brugada syndrome, Short QT syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia in the setting of the COVID-19 pandemic may prove particularly challenging. Depending on the inherited defect involved, these patients may be susceptible to pro-arrhythmic effects of COVID-19-related issues such as fever, stress, electrolyte disturbances and use of antiviral drugs. Hence, additional precautions and preventive measures are recommended, including ECG monitoring, aggressive antipyretic treatment, and more stringent social distancing to prevent infection.[10] We here describe the potential COVID-19 associated risks and therapeutic considerations for patients with distinct inherited arrhythmia syndromes and provide recommendations for their monitoring and management during this pandemic.

Long QT syndrome

The Long QT syndrome (LQTS) is characterised 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. LQTS is an inheritable condition caused by pathogenic variants in genes encoding ion channels (primarily *KCNQ1, KCNH2, SCN5A*).

An often-faced clinical situation, however, is acquired QT-interval prolongation, that occurs for instance during myocardial ischemia, hypothermia, as a result of treatment with a wide range of drugs, hypokalaemia or sepsis. Severe QTc-prolongation due to these conditions might similarly result in malignant arrhythmias. Rather commonly, patients who have severe forms of acquired QT-prolongation also have a genetic predisposition for QTc-prolongation,[11,12] but without such extreme provocation these patients generally have normal QT-intervals. In fact, many LQTS patients may also have QT-intervals within normal limits in resting conditions,[13] although this still puts them at higher risk for malignant arrhythmias,[14] especially during provocations such as the use of QTc-prolonging drugs.[15] Whereas severe forms of inherited LQTS often surface during (early) childhood (from infants to adolescents),[14,16] acquired QT-prolongation generally occurs in older patients because these critical provocative events more often occur in older patients.

Long QT syndrome and COVID-19

There are several issues that require attention when discussing COVID-19 in relation to inheritable or acquired QT-prolongation.

The most important determinant of risk for malignant arrhythmias in patients with LQTS or in acquired QT-prolongation, is the use of one or more QTc prolonging drugs in the setting of severe manifestations of COVID-19. Many drugs (either with cardiac or non-cardiac indications) have the ability to block cardiac potassium currents, impairing ventricular

repolarisation with subsequent prolongation of the QT-interval and an increased risk for malignant arrhythmias.[15] In addition, many drugs may alter drug metabolism, e.g. due to inhibition of CYP3A4, which may further increase plasma levels of QT-prolonging drugs and further increase risk. Of special interest in COVID-19 is that there are indications that chloroquine and hydroxychloroquine might be of value.[17]

Chloroquine is one of the most widely used anti-malarial drugs world-wide, but it has also been investigated as a potential broad-spectrum anti-viral drug.[18] Amongst its mechanisms, chloroquine appears to interfere with the terminal glycosylation of ACE2 and may thus negatively influence virus-receptor binding and abrogate infection.[19-21] However, chloroquine is closely related to quinidine, and while the latter is used as an anti-arrhythmic drug in Brugada syndrome and idiopathic forms of ventricular fibrillation, it is also well known for its QT-prolonging effects and has been associated with QT related malignant arrhythmias. Luckily, the QT-prolonging effect of chloroquine is very modest, and in general it does not result in clinically significant QT-prolongation in patients without LQTS.[22] Hydroxychloroquine sulfate, a less toxic derivative of chloroquine, is widely used in the chronic treatment of autoimmune diseases without significant effects on ECG parameters,[23] and was recently shown to also efficiently inhibit SARS-CoV-2 infection *in vitro*.[24] However, both chloroquine and hydroxychloroquine are metabolised by CYP3A4, and COVID-19 treatment with (hydroxy)chloroquine can be combined with additional anti-viral treatments such as ritonavir

plus lopinavir (both potent CYP3A4 inhibiting drugs; their combination is associated with QT-prolongation), azithromycin (besides a macrolide antibiotic also investigated for its antiviral properties, with also (weak) CYP3A4 inhibition and associated with QT-prolongation)[25,26], or remdesivir (an investigational drug for which metabolism and possible QT prolonging effects are not yet resolved). Combining (hydroxy)chloroquine with these drugs might thus result in higher plasma levels and significant QT-prolongation. Hence, we advise monitoring QT-intervals and cardiac rhythm if starting these drugs given the increased risk for malignant arrhythmias (Figure 1). In addition, physicians should be aware of the alpha-blocking effects of (hydroxy)chloroquine, which might result in hypotension.

Another issue is fever. The effect of fever is, in contrast to patients with for example BrS (see below), much less evident in patients with LQTS. A possible exception are patients, with specific LQTS 2 mutations, presenting with fever-triggered arrhythmias which are based on temperature sensitive mutant channels (i.e. less current with higher temperature).[27] As most patients hospitalised for COVID-19 have fever,[4] patients with known LQTS will thus generally not be at increased risk. The separate contribution of fever in acquired QT-prolongation is not well known, but sepsis is a denominator of risk of acquired QT-prolongation[28], and septic shock is one of the clinical scenarios in COVID-19.[4]

Finally, interpretation of the QT-interval is not easy,[29] but guidance is available.[13] While COVID-19 patients admitted to Intensive Care Units will often have continuous ECG

monitoring available, ECG monitoring of inpatients who are being treated in an airborne isolation room can be challenging. Nevertheless, if possible, we advise (Figure 1) to monitor QT-intervals at baseline and at 4h after administration of (hydroxy)chloroquine and/or anti-viral therapy in patients with congenital or acquired LQTS, patients already taking other QT-prolonging drugs, and patients with structural heart disease or bradycardia. A second ECG is recommended after 1-3 days. In all other patients, QTc-interval monitoring should be performed 24h after start of therapy. During the course of (hydroxy)chloroquine and/or anti-viral therapy, QTc-interval monitoring is furthermore indicated in case of worsening kidney/liver function and electrolyte disorders (in particular K^+, Ca^{2+} and Mg^{2+}), especially in LQTS patients or patients with abnormal QT-intervals at baseline. Of particular concern is the COVID-19 associated diarrhea which may lead to hypokalemia with adverse effects on the QTc interval. In addition, beta-blocker treatment should be considered if the patient is not yet treated. Cardiologists throughout Europe, Canada and the US have initiated a QT-interval registry for COVID-19 patients treated with chloroquine, hydroxychloroquine and/or anti-viral drugs and contribution is open to all.

In summary, we advise (Figure 1):

- QTc-interval monitoring when using (hydroxy)chloroquine in COVID-19 patients
- QTc-interval monitoring when using or combining anti-viral drugs in COVID-19 patients

- QTc-interval monitoring in patients with known LQTS, acquired QT-prolongation or conditions associated with acquired QT-prolongation (e.g. use of other QT-prolonging drugs, structural heart disease, bradycardia <50/min, liver and renal disease)
- When QTc is above 500msec, we advise consultation with a cardiologist ("QT-specialist") for guidance (which might, e.g., result in intensified monitoring, raising potassium levels, and/or discontinuation of one or more QT-prolonging drugs)
- Patients with acquired LQTS or patients using a combination of QT-prolonging drugs should have a high serum potassium level. Avoiding hypokalemia is not enough and the adagium should be "a serum potassium of 5 is better than 4."[30]

Brugada syndrome

Brugada syndrome (BrS) is a familial arrhythmia syndrome disorder characterized by the type 1 Brugada ECG pattern in the right precordial leads of the ECG (coved type ST-elevation and T wave inversion in lead V1 and/or V2) and an increased risk for ventricular fibrillation and sudden cardiac death. Up to 30% of patients with BrS carry a loss-of-function pathogenic variant (mutation) in *SCN5A*, the gene that encodes the cardiac sodium channel, as the pathophysiological substrate of their disease.[31] The most frequently used drugs for SARS-CoV-2 and COVID-19 patients are not on the list of drugs to be avoided by BrS patients.[32] However, attention to BrS patient management is relevant in the setting of the SARS-CoV-2 outbreak since ECG manifestations of the disorder may be uncovered during fever, and since fever has

been unequivocally associated with life-threatening arrhythmic events (LTE) in patients with the disorder.[33]

The importance of fever in BrS patients is now well-established.[33-35] In 24 patients with BrS, 3 of whom had a fever-triggered cardiac arrest, the increase in body temperature reduced the PR interval in control individuals, but increased PR interval, QRS width, and the maximum J-point in BrS patients.[34] Another study showed that fever-associated BrS seems to be associated with a higher future risk of LTE's compared to drug-induced type 1 pattern.[35] Finally, fever seems to be particularly relevant in children.[33] Indeed, in a registry with symptomatic BrS patients (the SABRUS registry) approximately 6% of LTE's were associated with fever and the highest rate of fever-triggered LTE's was observed in the very young (65%, age ≤5 years). In the age range 16 to 70 years, only 4% of the LTE's was related to fever. In the elderly (>70 years) this percentage increased to 25%.[33]

In the setting of fever, the presence of a pathogenic variant in *SCN5A* may be particularly relevant. In a single center series of 111 patients with BrS, 22 presented with a cardiac arrest, 4 of which were fever related. Three of these 4 patients harbored a pathogenic variant in *SCN5A*.[34] In the SABRUS registry, the percentage of *SCN5A* pathogenic variants was 77% in children and 27% in adults with a LTE.[33] The authors also performed an analysis of all published cases (up to 2018) with fever-triggered LTE's (40 patients in 22 reports) revealed the presence of a putatively pathogenic variant in *SCN5A* was found in 13 (68%) of 19 patients

tested.[33] Moreover, in a multicenter pediatric population of 106 patients, 10 patients had a LTE during follow-up, which was triggered by fever in 27%; all of the latter patients were positive for a pathogenic *SCN5A* variant. Finally, preliminary data in a pediatric cohort indicated that mainly children with a *SCN5A* mutation developed a type 1 ECG during fever (43.8% of children who developed a type 1 ECG during fever had a *SCN5A* mutation vs 4.2% of children without a type 1 during fever) and had events during follow-up (7/21 vs 0/47).[36] These studies collectively indicate that sodium channel function is sensitive to temperature. This sensitivity may be due to altered temperature-sensitive kinetics, in particular accelerated inactivation,[37] and/or decreased sodium channel expression at higher temperatures.[38] Also in other sodium channel mediated diseases, increased temperature sensitizes patients to disease-related symptoms.[39,40]

Based on the above we feel that the following recommendations are pertinent:

1. All patients with Brugada syndrome should self-treat with paracetamol/acetaminophen immediately if they develop signs of fever and self-isolate.
2. Patients without an ICD who are at higher risk due to fever include:
    a. sodium channel disease with or without a type 1 ECG pattern,
    b. children and young adults (under 26 years old) and the elderly (over 70 years) with Brugada syndrome; and

c. all patients with a spontaneous type 1 Brugada pattern and/or cardiac syncope.

3. If these higher risk patients develop a high fever (>38.5C) despite paracetamol treatment, they will need to attend the emergency department*. The emergency department must be forewarned to allow assessment by staff with suitable protective equipment. 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 ECGs show no sign of the type 1 ECG pattern, then they can go home to self-isolate.
4. 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 lowest risk and can afford to self-isolate at home. The risk of visiting the emergency department and contracting COVID-19 is likely to outweigh the risk of a LTE. Attendance at hospital should then be dictated by other clinical features, such as palpitations or (pre-)syncope etc. The same advice holds for patients with an ICD.

* attendance at the emergency department may require regulation according to the capacity of service and risk of COVID-19 infection.

** ideally three different ECGs with V1 and V2 in the 4th, 3rd and 2nd intercostal spaces

Management in the hospital should include monitoring of ECG abnormalities and arrhythmia, as well as efforts to reduce the body temperature (with antipyretic drugs, preferably paracetamol/acetaminophen, or eventually ibuprofen). More generally, BrS patients, in particular those with a pathogenic or likely pathogenic variant in *SCN5A*, are advised to self-isolate in their private environment.

Short QT syndrome

Short QT syndrome (SQTS) is a familial arrhythmia syndrome characterized by short QT intervals on the ECG and a significant rate of ventricular arrhythmias.[41] It is a heterogeneous disease caused by pathogenic variants in at least three different potassium channel genes (*KCNH2*, *KCNQ1* and *KCNJ2*) and the cardiac chloride-bicarbonate exchanger gene (*SLC4A3)*.[42] It is an extremely rare disease; in a recent systematic literature review only 110 cases were described.[43] No specific triggers for LTE, including fever, have been described. Hence, based on current knowledge, SQTS patients do not seem to be at particular risk when they are affected by COVID-19.

Potential drugs for COVID-19 patients, like chloroquine, might actually be beneficial for SQTS patients due to lengthening of their QT-interval, as has been suggested by modelling data for SQTS type 1 (*KCNH2*-related[44]) and type 3 (*KCNJ2* related[44,45]). There are no clinical data as far as we are aware.

We therefore do not believe that there is a particular concern when SQTS patients are infected with SARS-CoV-2.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a familial arrhythmia syndrome characterized by adrenergic-related ventricular arrhythmias (i.e. during exercise, or stress).[41] It is a heterogeneous disease with pathogenic variants in *RYR2* encoding the human Ryanodine receptor 2 as the most important contributor.[46] First line treatment comprises intensive beta blocker therapy. In insufficiently responsive cases flecainide should be added or left sympathetic denervation should be conducted.[41,46] ICD therapy should be avoided.[47]

As mentioned above, exercise and emotional circumstances constitute specific triggers for LTE. An increased heart rate alone (pacing-induced), as an important symptom of fever, does not appear to be sufficient for the induction of ventricular arrhythmias.[48] Fever, as a specific trigger has not been described. Whether or not the stressful circumstances that COVID-19 patients find themselves in will lead to an increased burden of arrhythmias can only be speculated upon.

The antiviral therapy proposed for COVID-19 is not expected to lead to increased risk. The only potential deleterious pharmacological interaction in these patients are drugs with alpha or beta adrenoceptor mimetic activity, which may be used in cases in need of hemodynamic support. Intravenous epinephrine has been used to unmask ventricular

arrhythmias and initial data suggested that epinephrine was more effective than exercise testing in unmasking ventricular arrhythmias.[49] Later studies revealed, however, a low sensitivity and high specificity (with the exercise test as the gold standard[50]). Nevertheless, based on their pathophysiological mechanism of action, epinephrine, isoproterenol and dobutamine, all alpha and/or B1 receptor agonists, should probably be avoided. Milrinone, the most widely used phosphodiesterase 3 inhibitor, acts by decreasing the degradation of cyclic adenosine monophosphate (cAMP). This may potentially stimulate the RyR2 receptor and must thus be used with caution. However, with continuation of the beta blockers (as we recommend, see below) this may not be that relevant because betablockers suppress milrinone-induced increased Ca-leak.[51] CPVT patients, in particular those who were symptomatic prior to diagnosis, should stay on their beta blocker treatment with or without flecainide as long as is tolerated hemodynamically. Flecainide does have interactions with Ritonavir/Lopinavir and chloroquine, yet we believe that it is an important enough therapy not to stop in these particularly stressful circumstances.

Based on the above we also suggest avoidance of epinephrine in the setting of a VT/VF arrest if possible. This is probably the only resuscitation setting where epinephrine is contraindicated.[52]

Conclusion

Patients with inherited arrhythmia syndromes may be at an increased pro-arrhythmic risk in the setting of COVID-19 infection, necessitating additional precautions and specialized management. Preventive measures should include stringent social distancing to prevent infection, aggressive antipyretic treatment to reduce fever in Brugada syndrome patients, and ECG monitoring in Long QT syndrome patients treated with antiviral drugs.

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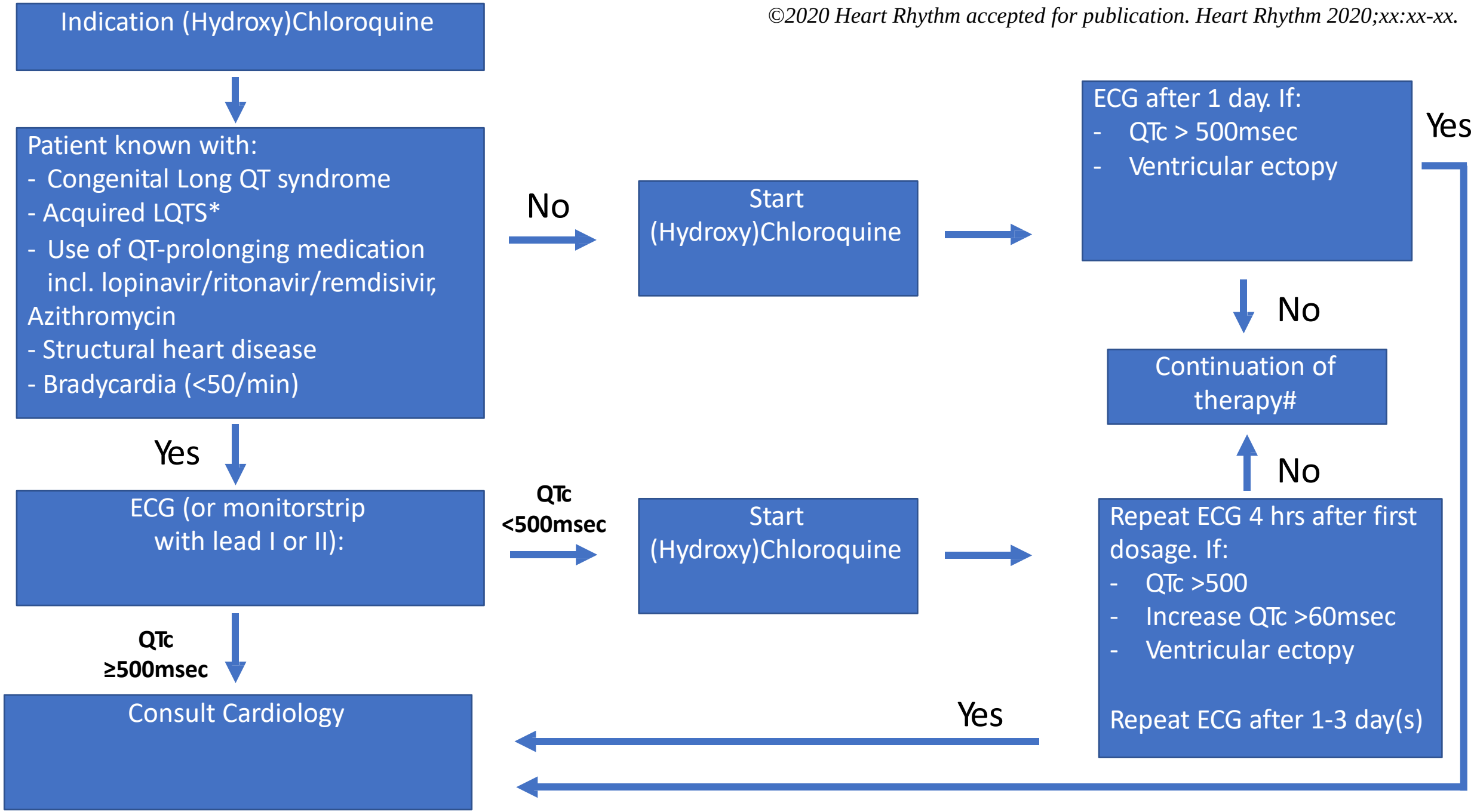
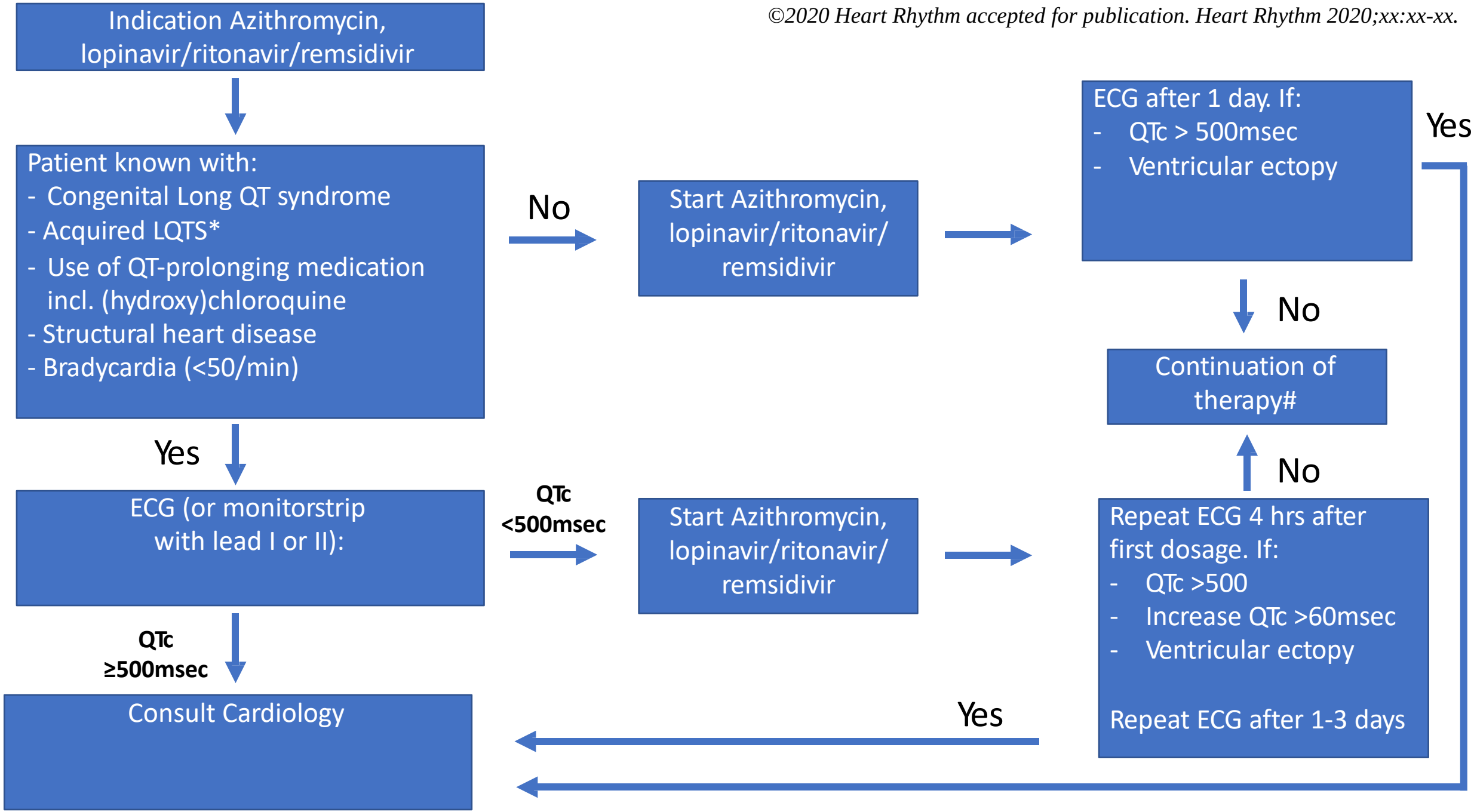
Figure legends

Figure 1: Flowchart of proposed guidance of QTc monitoring in patients receiving (hydroxy-)chloroquine and/or antiviral drugs and /or azathromycin. It should be noted that not every LQTS patient has the same risk. The length of the QTc interval is of importance (as is implicit in the flowchart) but also gender, age and the genotype are important. LQT2 patients may be at higher risk than LQT1 patients for example. The consulted cardiologist should have sufficient experience with QT-related arrhythmic problems.



*: earlier QTc prolongation with medication; #: if ventricular ectopy, arrhythmia, dizziness or loss of consciousness: consult cardiology



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