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Recommendations for the Management of COVID 19 Patients Regarding Proarrhythmic Effects of Some Current Treatments, Specifically if These Patients Suffer From Arrhythmias, and for Those Receiving Antiarrhythmic Therapy. Eurasian Arrhythmology Association (EURA), Argentinean Society of Arrhythmias (SADEC), European Cardiac Arrhythmia Society (ECAS)

Recommendation provides information to employees of medical departments at any level and primarily primary care about the possible proarrhythmic and adverse effects of drugs used for the treatment of COVID-19 patients and the features of therapy for COVID-19 patients with heart rhythm and conduction disorders receiving permanent antiarrhythmic therapy. Aim: provide information to employees of medical departments at any level and primarily primary care about the possible proarrhythmic and adverse effects of drugs used for the treatment of COVID-19 patients and the features of therapy for COVID-19 patients with heart rhythm and conduction disorders receiving permanent antiarrhythmic therapy.

Keywords Coronavirus infection (COVID-19); antiarrhythmic therapy; hydroxychloroquine; QT interval; polymorphic ventricular tachycardia torsades de pointes

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1. Introduction

The COVID-19 (COronaVIrus Disease 2019) pandemic is a serious challenge to the global healthcare system, as millions of people are infected and there are currently no drugs with proven clinical efficacy [1]. The list of drugs with a proposed positive effect in patients with COVID-19, used «off-label», despite the lack of accurate data on their effectiveness, usually includes chloroquine/hydroxychloroquine, protease inhibitors (usually lopinavir-ritonavir) and azithromycin [2–4].

One of the main problems with treatment with these drugs is the risk of prolongation of the corrected QT

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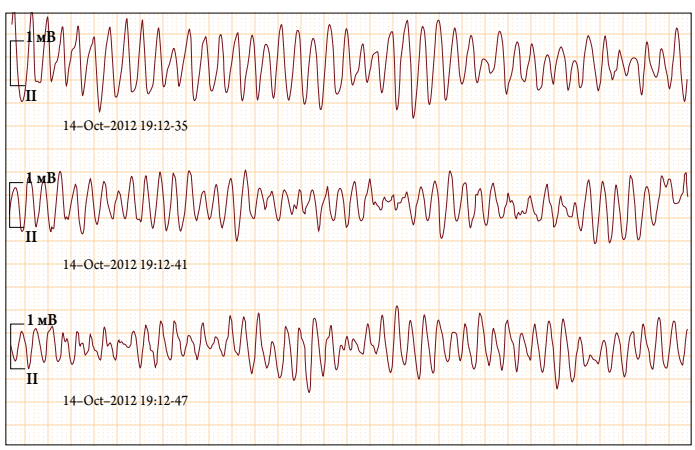
interval (QTc) with the development of life-threatening ventricular tachycardia torsades de pointes. This risk may be significantly increased in patients with COVID-19 due to a number of factors: direct damage to the myocardium as a result of an inflammatory cascade or cytokine release; acute coronary syndrome due to atheroma destabilization caused by inflammation; microvascular damage due to disseminated intravascular coagulation and thrombosis; direct penetration of the virus into cardiomyocytes by binding to angiotensin-converting enzyme 2 (ACE2) receptors; hypoxemia in combination with increased metabolic needs of the heart, which leads to myocardial damage similar to type 2 myocardial infarction [5–7]. During COVID-19, the risk of prolongation of the QTc interval can significantly in the presence of previously existing or transient bradycardia, as well as with simultaneous administration of QT-lengthening drugs and/or electrolyte disbalance (hypokalemia, hypomagnesemia). On the one hand, COVID-19 itself (fever, hypoxia, adrenergic tone, etc.) provokes arrhythmias, which are treated with antiarrhythmic drugs, while on the other hand, patients can receive previously prescribed antiarrhythmic pharmacotherapy, to which they add drugs that are presumably effective in the case of COVID-19. The overall effect of the combination of these drugs on the duration of the QTc interval in patients with COVID-19 may be significantly more pronounced. Available data on the potential interaction of experimental COVID-19 therapy with risk of QT prolongation and ventricular tachycardia torsade de pointes are available at. In such a situation, medical decisions will be effective and safe only if both benefits and risks of drug interactions are taken into account.

2. QT interval evaluation

The QT interval is the time interval of the surface ECG from the beginning of the Q wave to the return of the descending knee of the T wave to the isoline, reflecting the processes of depolarization and repolarization of the ventricular myocardium. Prolongation of the QT interval is associated with syncope and a high risk of sudden cardiac death due to torsades de pointes ventricular tachycardia.

Figures 1. Paroxysm of torsades de pointes in a 50-year-old patient with long QT syndrome



Torsades de pointes polymorphic ventricular tachycardia is characterized by frequent and irregular wavelike changes in the amplitude of QRS complexes, which in prolonged episodes resemble the shape of a spindle. Extending the QT interval significantly increases the risk of torsades de pointes, but this relationship is not linear. A number of studies confirm that in patients who have undergone torsades de pointes, the duration of the QT interval is comparable to the value of this indicator in patients who registered only single ventricular extrasystoles [8]. The most episodes of torsades de pointes are terminated spontaneously, but there is always a risk of their transformation to ventricular fibrillation, which requires considering this form of tachycardia as prognostically extremely unfavorable [9] (Fig. 1).

According to the AHA/ACCF/HRS Recommendations for standardization and interpretation of ECG, the QT interval should be measured in all 12 ECG leads, and the lead with the longest QT interval value (usually V2 or V3) should be used in further calculations. If the duration of the QT interval in this lead exceeds its duration in other leads by more than 40 ms, the measurement may be considered incorrect and it is suggested to use the QT value in one of the standard leads [10].

It is known that the duration of the QT interval is not constant and is inversely dependent to the heart rate (HR), which makes it necessary to calculate the QTc. To calculate QTc, the Bazett formula

$$(QTc = QT/\sqrt{\ }RR),$$

which was introduced in 1920, is traditionally used. It can be replaced by several dozen other formulas, the most common of which are Fridericia, Framingham, Hodges and Spline (Rabkin) [11]. The normal and increased values of the QT interval calculated using these formulas are shown in Table 1.

Certain difficulties arise when evaluating the QT interval in patients with slow intraventricular conduction (e.g. His bundle block, presence of ventricular pacing). The duration of the QT interval in these patients is increased due to the broadening of the QRS complex, but this should not automatically refer them to the group of patients with high arrhythmic risk. When calculating the duration of the QT interval in such patients the Boghossian formula is the most convenient

$$QTc = QTc_{LBB/paced} - 50\% \times QRS_{LBBB/paced}.$$

We can also use the formula:

$$QTc = QTc - (QRS - 100\ ms),$$

where LBB is left bundle block.

Thus, the QT interval of a patient with constant ventricular stimulation (with a base frequency of 60/min), on the ECG shown in Fig. 2, exceeds 500 ms, but a significant part of it is a deformed QRS complex. Using the Boghossian formula, we get QTc= 540– (200*50%) = 440 ms, which is within normal range values.

3. Clinical status assessment in COVID-19 patients

The severity assessment is carried out by a combined assessment of the severity of symptoms, clinical data, and x-ray images. The severity of lung damage on a CT scan correlates with the severity of the disease, so it seems rational to assess the involvement of lung tissue.

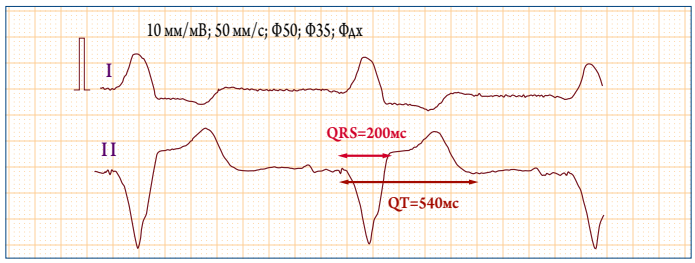
Mild course of the disease indicates the presence of not more than 3 lesions of ground-glass opacity (GGO), on intermediate – more than 3 lesions or sections GGO, and severe – GGO in conjunction with mixed consolidation or complete consolidation with reticular changes [12].

4. Medications for treatment of COVID-19 which prolong the QT interval in patients who have not previously received antiarrhythmic therapy

4.1 Low risk category of arrhythmogenic and proarrhythmic effects

According to the protocol published by the Mayo Clinic on March 25, 2020, this group of patients includes COVID-19 patients with a QTc Bazett interval of <470 ms for men, <480 ms for women, and <460 ms for children under the age of 17 without the presence of concomitant risk factors.

Figures 2. ECG of 70-year old patient with an implanted pacemaker (DDD = 60), permanent ventricular pacing with basic frequency 60 b.p.m.



- Congenital LQTS.
- Acquired LQTS (earlier QTc prolongation with any medication).
- Constant use of QT-prolonging medications (antiarrhythmic agents, anticancer drugs, etc.).
- Use of QT-prolonging drug in COVID-19 therapy (incl. azithromycin, hydroxychloroquine, lopinavir/ritonavir).
- Structural heart disease.
- Bradycardia (HR < 50 b.p.m.).
- Hypokalemia (< 3.5 mmol/L).
- Chronic renal and (or) hepatic failure.

It is believed that such patients have a low probability of ventricular arrhythmias and hydroxychloroquine (or another QT prolonging drug) can be prescribed to them directly after an ECG recording with the calculation of the corrected QT interval [13]. If after administration of hydroxychloroquine on the next day, the ECG shows a prolongation of the QT interval over 500 ms and (or) ventricular extrasystole appears, it is advisable to stop using it (Fig. 3, 4).

4.2. Moderate risk category of arrhythmogenic and proarrhythmic effects

The moderate risk group for ventricular arrhythmias should include patients with COVID-19 and QT interval prolongation not exceeding 500 ms, as well as patients with concomitant risk factors (see Table 2). In such

Table 1. Values of the corrected QT interval applying the most frequently used formulas for measuring QTc

QT corrected estimation formula	Normal QTc, ms		Borderline QTc, ms		Prolonged QTc, ms	
	males	females	males	females	males	females
Bazett ($QTc = QT/\sqrt{RR}$)	<430	<440	430–450	440–460	>450	>460
Fridericia ($QTc = QT/\sqrt[3]{RR}$)	<429	<438	429–441	438–451	>441	>451
Framingham ($QTc = QT + 0{,}154 \times (1 - RR)$)	<428	<438	428–440	438–450	>440	>450
Hodges ($QTc = QT + 105/RR - 105$)	<428	<436	428–441	436–449	>441	>449
Spline-formula	<430	<430	430–442	430–442	>442	>442

$QTc(Spline) = 523.29 - 76.94*B1(HR) - 101.59*B2(HR) - 130.81*B3(HR) - 144.79*B4(HR) - 196.76*B5(HR) - 231.01*B6(HR) - 247.84*B7(HR) + 9.35*female + 0.18*age$, *where* $B1(x) - B7(x)$ are seven orthogonal b-spline basis functions, taking HR as their argument and allowing for a non-linear regression relationship to be fit between HR and QT.

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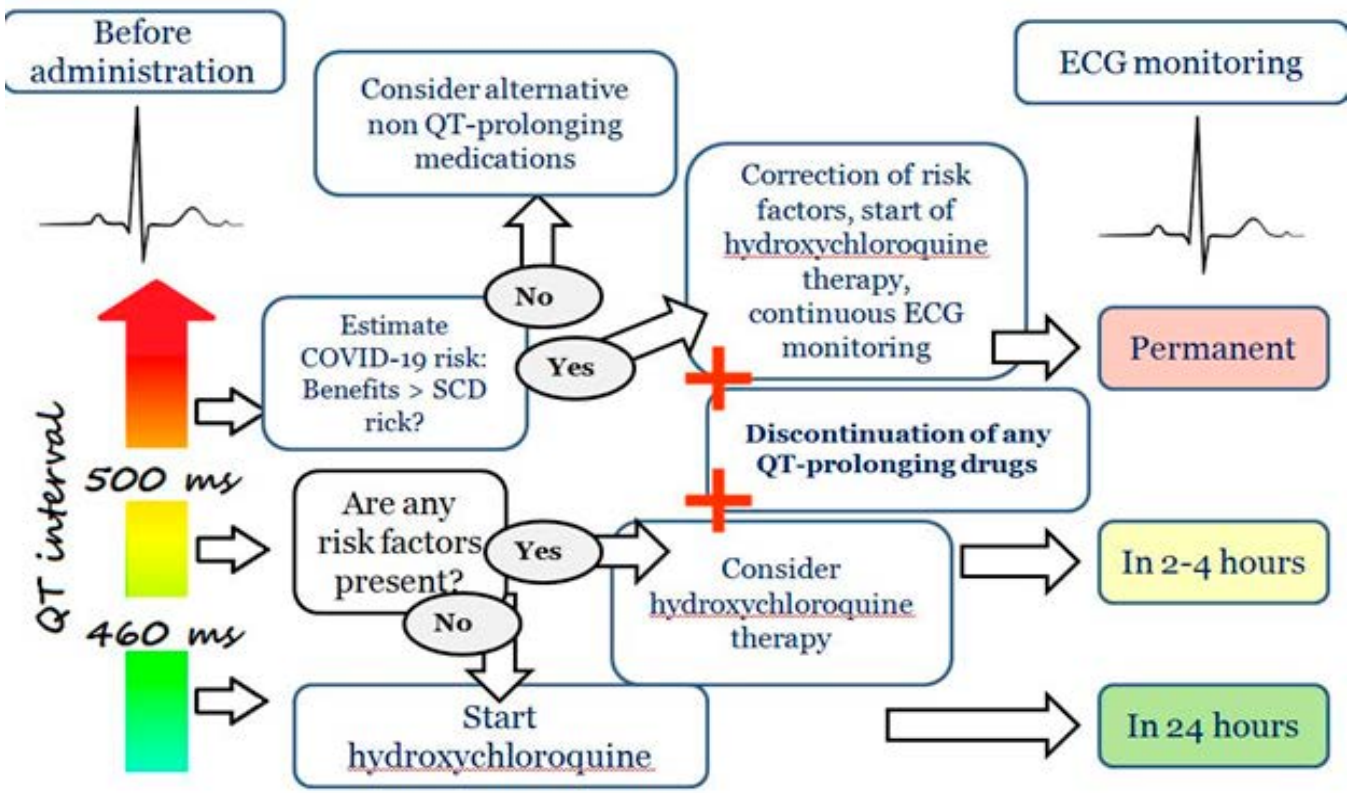
Figures 3. The algorithm for the administration of hydroxychloroquine, based on the duration of the QT interval and the risk factors of TdP



patients, efforts should be made to correct concomitant electrolyte abnormalities (primarily hypokalemia). In mild COVID-19 (not more than 3 lesions of GGO) any drugs which prolong the QT interval should be discontinued, if those drugs are not essential to provide symptomatic relief to the patient (antihistamines, sedatives, etc.). Thus, in younger patients with mild course of COVID-19 and a significant prolongation of the QTc interval, it is advisable to discontinue treatment, as the risk of developing threatening arrhythmias may outweigh the risk of developing acute respiratory distress syndrome associated with COVID-19.

However, in moderate course (more than 3 lesions of GGO) and severe course (GGO in conjunction with mixed consolidation or complete consolidation with reticular changes) and older patients (60–65 years and older) with progressive deterioration of respiratory symptoms or concomitant diseases at high risk of respiratory complications (chronic obstructive pulmonary disease, bronchial asthma, renal dysfunction, obesity, diabetes mellitus, chronic heart failure), the benefit of prescribing medications that lengthen QTc may exceed the risk of ventricular arrhythmias. In such cases, after maximum correction of risk factors, the administration of these agents, including hydroxychloroquine, should be considered, followed by ECG monitoring every 2–4 hours after administration (Fig. 3). A beta-blocker (preferably nadolol) can be added to the therapy regimen at a therapeutic dose. If the ECG shows an elongation of the QT interval over 500 ms or an increase in the QT interval dispersion over 60 ms and (or) ventricular extrasystole appears, it is also advisable to stop using them (Fig. 4).

4.3. High risk category of arrhythmogenic and proarrhythmic effects

Patients with an interval of longer than 500 ms (with QRS less of equal to 120 ms) are at increased risk of further prolongation of the QT interval and the occurrence of polymorphic ventricular tachycardia. The decision to prescribe therapy that prolongs the QT interval, such as hydroxychloroquine, in this situation should be made collectively by a team of doctors with mandatory participation of a cardiologist. If a decision is made to prescribe therapy which increases the QT interval in such patients, it should be possible to constantly monitor the ECG by all available means (bedside monitor, wearable recorders, including gadgets) and immediately use an

automatic external defibrillator, which means that it can be placed in close proximity to the patient (Fig. 3, 4).

4.4. Combined administration of drugs that extend the QT interval and the risk of arrhythmogenic and proarrhythmic effects

An urgent issue is the possibility of combination of two or more drugs that increase the QT interval (for example, hydroxychloroquine and azithromycin). In a number of studies, combinations of drugs that prolong the QTc interval did not cause a greater degree of QTc interval increasing than taking a single drug (for example, domperidone and ondansetron) [14, 15]. However, in a recent study by A. Meid et al. it is concluded that drugs with a confirmed (but not probable or conditional) risk of torsades de pointes according to the AZCERT classification have an additive effect on the duration of the repolarization phase [16]. Thus, if there are risk factors for fatal arrhythmia (see Table 2), it is advisable to avoid prescribing such combinations of drugs, and if this is not possible, then prescribe them for the shortest possible time, while constantly monitoring the ECG and the level of electrolytes in the blood. With a light course of COVID-19 (the presence of no more than 3 lesions of GGO), one should, if possible, avoid prescribing any drugs that lengthen the QT interval. In moderate and severe course of COVID-19 (see Section 3), as well as in older patients (60–65 years and older) with progressive deterioration of respiratory symptoms or concomitant diseases of high risk of respiratory complications, the benefit of combined administration of QTc prolonging drugs may exceed the risk of ventricular arrhythmias. In such cases, after maximum correction of risk factors, the combined administration of these agents should be considered collectively, with the mandatory participation and control of cardiologists.

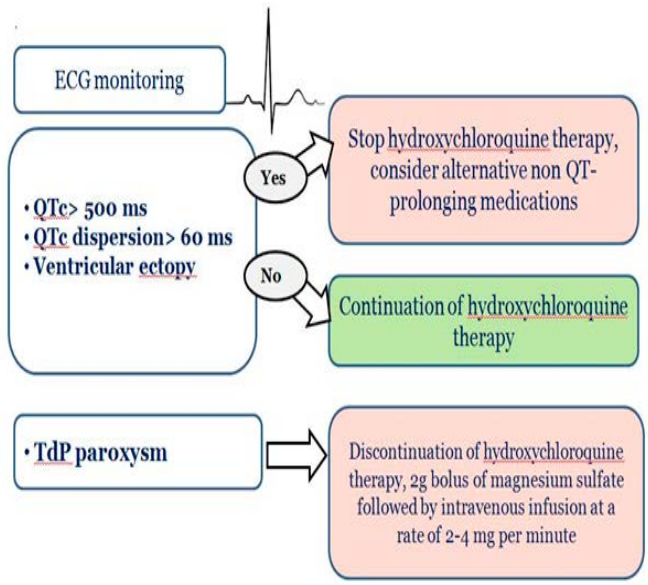
To calculate the risk of QT prolongation in patients in intensive care units, we suggest using the Tisdale scale developed in 2013 [17] (see Table 2).

Patients who scored less than 7 points are at low risk for drug-induced QT interval prolongation and associated ventricular arrhythmias, from 7 to 11 points are at moderate risk, and more than 11 points are at high risk.

4.5. Practical recommendations for prescribing drugs that extend the QT interval for treatment of patients with COVID-19 who have not previously received antiarrhythmic therapy

Currently, there is no proven effective therapy for COVID-19, and its effects on other diseases, in particular heart rhythm disorders, also remain unclear.

Figures 4. The algorithm for the administration of hydroxychloroquine, based on the ECG monitoring data



TdP – torsades de pointes

Experimental strategies for treating pneumonia should be decided on with consideration of the possibility of prolonging the QT interval. A differentiated approach should be used when prescribing treatment. With a light course of COVID-19, one should avoid prescribing any medications that lengthen the QT interval. In moderate to severe cases, as well as in older patients (60–65 years and older) with progressive deterioration of respiratory symptoms or concomitant diseases of high risk of respiratory complications, the benefit of prescribing drugs that lengthen the QTc may exceed the risk of ventricular arrhythmias. The decision to prescribe treatment in such cases should be individualized and decision-making on the use of drugs should be made collectively.

Table 2. Tisdale score

Risk factor	Points
Age ≥ 68 years	1
Female sex	1
Loop diuretic	1
Serum K+ ≤ 3.5 mEq/L	2
Admission QTc ≥ 450 ms	2
Acute MI	2
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Two and more QTc-prolonging drugs	6
Maximum Risk Score	21

K+ = potassium; MI = Myocardial infarction

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Based on the above data, the organizational and scientific committees, as well as the Board of Trustees of the Eurasian Arrhythmological Association (EURA), offer the following recommendations for the practical clinical use of drugs for the treatment of patients with COVID-19 who have not previously received antiarrhythmic therapy.

Recommendations for the management of patients with coronavirus infection (COVID-19) and QT prolongation

1. For each patient with a coronavirus infection (COVID-19) at admission, it is necessary to record a standard ECG with the calculation of the QT interval and the corrected QT interval using any of the formulas proposed for standardization.
2. It is necessary to achieve the maximum elimination of risk factors for prolongation of the QT interval, to correct the electrolyte metabolism (especially in patients with symptoms of diarrhea), to conduct daily monitoring of the level of potassium in the blood plasma.
3. It is necessary to cancel any medications that extend the QT interval, but are not vital for the patient.
4. In patients with impaired intraventricular conduction and implanted intraventricular devices with constant ventricular stimulation, to eliminate the risk of hypercorrection when calculating the corrected QT interval, use the Bogossian formula (or another formula developed for such patients).
5. Stratification of the risk of life-threatening arrhythmias in patients in inpatient departments should be carried out with taking into account the duration of the QT interval and associated risk factors, in patients in the department of anesthesiology-intensive care-using the Tisdale scale; the risk level should be taken into account when prescribing therapy for coronavirus infection (COVID-19).
6. If paroxysm torsades de pointes occurs, the use of hydroxychloroquine, azithromycin and other drugs that lengthen the QT interval should be immediately discontinued, for relief, use intravenous bolus administration of 2 g of 25% solution of magnesium sulfate followed by drip administration at a rate of 2–4 mg per minute (class IIA indications).

5. Administration of drugs that extend the QT interval in patients receiving antiarrhythmic therapy

Experimental strategies for treating COVID-19-induced pneumonia should be implemented with caution in patients already receiving antiarrhythmic therapy. The potential risk of a dangerous interaction between antiarrhythmic drugs and COVID-19 treatments for the occurrence of ventricular proarrhythmia due to prolongation of the QT interval should be divided into high (co-administration of drugs should be excluded), moderate (dose adjustment and careful monitoring are required), and low (dose adjustment is required, but careful monitoring is usually not necessary). Available data on the potential interaction of COVID-19 experimental therapy with respect to the risk of QT prolongation and ventricular tachycardia torsades de pointes are available at https://www.covid19-druginteractions.org.

5.1. High risk of drug interaction

Chloroquine/hydroxychloroquine have a high risk of interaction with dofetilide, sotalol, amiodarone, flecainide, and mexiletine.

Azithromycin has a high risk of interaction with dofetilide, sotalol, amiodarone, flecainide, disopyramide, and propafenone.

Lopinavir-ritonavir has a high risk of interaction with dofetilide, sotalol, amiodarone, dronedarone, flecainide, and disopyramide.

5.2. Moderate risk of drug interaction

Chloroquine/hydroxychloroquine have a moderate risk of interaction with quinidine, disopyramide, propafenone, and digoxin.

Azithromycin has a moderate risk of interaction with beta-blockers and digoxin.

Lopinavir-ritonavir has a moderate risk of interaction with lidocaine, mexiletine, propafenone, quinidine, beta-blockers, verapamil, diltiazem, and digoxin.

5.3. Low risk of drug interaction

Chloroquine/hydroxychloroquine has a low risk of interaction with beta-blockers and verapamil.

Tocilizumab has a low risk of interaction with amiodarone and quinidine.

There are no data about the negative cardiotropic interaction of ribavirin and remdesivir with the pharmacotherapy of arrhythmias.

5.4. Strategy of antiarrhythmic treatment of patients with COVID-19

The choice of antiarrhythmic treatment tactic should be based on previously developed clinical recommendations. In order to prevent iatrogenic prolongation of the QTc interval and ventricular tachycardia torsades de pointes during COVID-19 pharmacotherapy, special guidelines have been developed [13]. Considering the listed risks and indications for the use of certain antiarrhythmic drugs for certain heart rhythm disorders, we can

assume possible options for medical tactics in relation to COVID-19.

5.4.1. Relapse of atrial fibrillation/flutter

Relapse of atrial fibrillation/flutter is more likely in COVID-19, which is a complex provoking factor (hypokalemia, hypomagnesemia, metabolic acidosis, use of dobutamine and dopamine, hardware artificial ventilation, volume overload, increased sympathetic tone, inflammation, ischemia, bacterial superinfection and myocardial damage), and is associated with a worse prognosis [18].

When hemodynamic instability occurs due to atrial fibrillation/flutter, amiodarone is the antiarrhythmic drug of choice for restoring and maintaining sinus rhythm, but its combination with hydroxychloroquine and/or azithromycin should be avoided. When considering the use of amiodarone, the intended benefit of treatment should exceed the risk of proarrhythmia due to the prolongation of the QT interval. In hospitalized patients with COVID-19 receiving antiviral treatment and recurrent atrial fibrillation/flutter without hemodynamic instability, discontinuation of antiarrhythmic medications (sotalol, amiodarone, propafenone, flecainide) may be preferable. After their cancellation, therapy is indicated to control the frequency of ventricular contractions using beta-blockers (or verapamil or diltiazem) in the absence of contraindications, in combination with digoxin or without it, considering the drug interaction. After recovery from COVID-19, the arguments for choosing to control ventricular rate or restore and maintain sinus rhythm should be re-evaluated.

5.4.2. The first manifestation of malignant ventricular arrhythmia

The first manifestation of malignant ventricular arrhythmia in COVID-19 is a marker of acute myocardial damage and may require more aggressive immunosuppressive and antiviral treatment. In patients with cardiovascular disease and a history of ventricular arrhythmias, COVID-19 may play a role as a trigger for ventricular tachycardia/ventricular fibrillation [7].

With stable monomorphic ventricular tachycardia in patients taking antiviral drugs that lengthen the QT interval, especially in cases of artificial ventilation, electrical cardioversion should be considered; with relatively stable hemodynamics in patients receiving antiviral drugs that lengthen the QT interval, intravenous administration of procainamide or lidocaine can be considered; in case of structural heart disease and pre-existing left ventricular dysfunction, intravenous administration of amiodarone may be considered (its combination with hydroxychloroquine and azithromycin should be avoided due to its effect on the duration of the QTc interval). The benefit of the planned treatment should exceed the risk of proarrhythmia due to prolongation of the QT interval.

In patients with severe COVID-19 and recurrent persistent ventricular tachycardia/recurrent ventricular fibrillation, amiodarone is the antiarrhythmic drug of choice. However, its combination with hydroxychloroquine and/or azithromycin should be avoided, and the benefit of treatment should exceed the risk of proarrhythmia due to the prolongation of the QT interval. It is advisable to add beta-blockers (for example, esmolol) and sedation.

5.4.3. Prevention of torsades de pointes ventricular tachycardia

Prevention of torsades de pointes ventricular tachycardia in COVID-19 is particularly relevant in the treatment of QT-prolonging antiviral drugs (hydroxychloroquine and azithromycin) in combination with antiarrhythmic drugs (especially sotalol), electrolyte disorders (hypokalemia, hypomagnesemia), kidney dysfunction and/or bradycardia, especially in women, patients with hypertrophy and/or reduced contractile function of left ventricle. To prevent a recurrence of ventricular tachycardia, it is necessary to discontinue all drugs that lengthen the QT interval, ensure the level of potassium in the blood serum more than 4.5 mmol/L, inject intravenous magnesium sulfate, increase heart rate by stopping bradycardic agents and, if necessary, apply isoproterenol (contraindicated in the syndrome of congenital prolongation of the QT interval) or temporary overdrive pacing.

6. Risks of drug interaction of antibiotics used for the treatment of COVID-19 with antiarrhythmic drugs

6.1. Risk of torsades de pointes

Macrolides and fluoroquinolones are drugs that cause a dose-dependent prolongation of the QT interval and have a proven risk of torsades de pointes, so their combination with class 1A, class 1C (flecainide) and class III antiarrhythmics is contraindicated. Isolated cases of torsades de pointes have been described for metronidazole, co-trimoxazole and piperacillin-tazobactam, so their combined use with the above-mentioned antiarrhythmic drugs is undesirable [19–22].

6.2. Effects on cytochrome P-450

Most antiarrhythmic drugs are metabolized in the liver using cytochrome P-450, so antibiotics acting as

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inducers or inhibitors of isoenzymes of this cytochrome affect the concentration and effects of antiarrhythmics.

Thus, some macrolides (clarithromycin, erythromycin and troleandomycin) are strong inhibitors of the CYP3A4 isoenzyme, and their administration leads to an increase in plasma concentration and increased side effects of propafenone (proarrhythmic effects), verapamil and diltiazem (hypotension, bradycardia, atrioventricular block) that are metabolized using this isoenzyme [23]. A safer alternative in such cases may be azithromycin.

Ciprofloxacin, as a strong inhibitor of the CYP1A2 isoenzyme, increases the concentration of mexiletin in blood plasma and increases the risk of its side effects (dizziness, tremor, proarrhythmogenic effects) [24]. Therefore, an alternative option may be to prescribe another antibiotic from the group of fluoroquinolones.

Rifampicin, considered as a potential agent for COVID-19 therapy, being an inducer of the CYP2D6 isoenzyme, accelerates metabolism, reduces plasma concentration and therapeutic effects of mexiletin, propafenone, etacizine, allapinin, lipophilic beta-blockers (carvedilol, metoprolol, propranolol), amiodarone, sotalol, verapamil and diltiazem [25], which limits the possibility of its use in patients receiving antiarrhythmic therapy.

6.3. Other effects of antibiotics

The polypeptide antibiotic linezolid, used in the treatment of secondary infections in patients with COVID-19, has the properties of a weak MAO inhibitor, which when co-administered with beta-blockers can lead to the development of orthostatic hypotension due to a functional block of sympathetic neurotransmitters, so with such a combination of drugs, blood pressure should be monitored, especially in the first week of treatment.

The combined use of linezolid and amiodarone increases the risk of development and progression of peripheral polyneuropathy, especially in patients with diabetes and over the age of 60, so it is not desirable to use them for a long time

No conflict of interest is reported.

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