

Evaluation and follow-up of pediatric COVID-19 in terms of cardiac involvement: A scientific statement from the Association of Turkish Pediatric Cardiology and Pediatric Cardiac Surgery

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Introduction

This guide has been prepared specifically for the benefit of pediatric cardiologists and pediatricians to guide the management against the new Coronavirus disease-2019 (COVID-19), which emerged in Wuhan City, China in December 2019, before spreading all over the world and becoming a pandemic.” Studies from several countries have confirmed that COVID-19 infection causes mild symptoms, and that severe illness and death resulting from COVID-19 is extremely rare among children (1-6). Thus, physicians dealing with pediatric patients have relatively fewer and less severe patients. Although children with COVID-19 are usually asymptomatic or mildly symptomatic, they may be highly contagious even in these cases (3, 6).

For this reason, the pandemic concerns not only the physician on duty for management of the infected child, but also physicians who care for pediatric patients in all specialties. It is currently not possible to foresee how long the pandemic will continue, how many people will be affected, and whether there will be recurrences, even in the most ideally managed scenario. Each day, the number of new cases is increasing both in our country and around the world. During the preparation of this

manuscript, the number of confirmed COVID-19 cases had exceeded 4 million cases worldwide, with 150.000 cases in Turkey. COVID-19 disease is also seen in both children and adults with congenital heart disease owing to the natural course of the infection. Thus, it would be beneficial to develop a guideline for the management of pediatric patients during the pandemic with an emphasis on cardiac evaluation and follow-up of these patients.

In the first part of this guideline (Part A), we provide an evaluation of the cardiovascular system and management of complications in children who experienced COVID-19 infection without underlying cardiac disease. In the second part (Part B), we discuss the follow-up and treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children with congenital or acquired heart disease.

The number of cases requiring hospitalization and intensive care among pediatric patients is extremely low (1-6). Accordingly, comprehensive series including a large number of pediatric cases regarding clinical course and management of COVID-19 have not yet been published at the time of developing this guideline, and we have relied on limited publications and data (1-6). For this reason, while developing COVID-19 follow-up and treatment recommendations during this study, evaluations and sug-

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gestions were made from the perspective of pediatric cardiology and congenital heart diseases with consideration to adult studies and guidelines. It has also been noted that this guideline is compatible with the COVID-19 (SARS-CoV-2 infection) guideline published by the General Directorate of Public Health, Ministry of Health, Turkey (7).

Part A: Cardiac evaluation in pediatric COVID-19

A careful family and contact history are taken, and cardiovascular system examination is performed along with vital signs (e.g., heart rate, respiratory rate, blood pressure, and oxygen saturation), as is usual in the case of other general infectious diseases that are evaluated for heart involvement. In these patients, sinus tachycardia accompanied by fever or hypoxia is frequently observed, and tachycardia incompatible with fever should be considered in terms of cardiac involvement. It should be remembered that complaints such as tachycardia, tachypnea, dyspnea, hypoxia, fever, and cough can be seen in COVID-19, as well as other congenital and acquired heart diseases. If physicians are focused only on COVID-19 while evaluating pediatric patients, other heart diseases such as congenital heart diseases, myocarditis, pericarditis, Kawasaki disease, and acute rheumatic fever, might be overlooked.

There is no need for a special cardiac examination in patients whose clinical condition is stable and can be followed up as outpatients. In addition to routine laboratory examinations, troponin I and T, and brain natriuretic peptide (BNP)/N-terminal pro-b-type natriuretic peptide (NT-proBNP) tests can be conducted in patients who are not clinically stable and may need hospitalization. For example, if the patient has a finding suggesting myocardial injury [chest pain, ST-T segment change in electrocardiogram (ECG)], troponin can be performed. If there are signs of heart failure, BNP/NT-proBNP assays can be performed. A high troponin level indicates myocarditis or myocardial injury, and elevated BNP levels indicate heart failure secondary to myocardial injury (7-10).

ECG is recommended in cases that have tachycardia incompatible with fever and rhythm abnormalities. Prolonged PR interval on ECG, ST-T segment changes, atrioventricular block, arrhythmia, tachycardia, and low voltage are findings suggestive of cardiac injury. ECG should be performed for "corrected QT" (QTc) measurement in patients who start medication that may lead to QT prolongation and arrhythmia, such as hydroxychloroquine and azithromycin. Unnecessary routine ECG should be avoided to prevent contamination (7, 10).

Echocardiography (ECHO) is performed in patients with heart failure, cardiomegaly, tachycardia incompatible with fever, ST-T segment changes, and arrhythmia in ECG. Because there will be a long period of close contact between the patient and the physician during the ECHO procedure, it is recommended to avoid performing an ECHO without indication in order to protect the physician from contamination (8-10). At the same time, the risk of transmission from patient to patient

will increase as the disinfection of the probes, the instruments, and physical environment may be insufficient when frequently used. All patients during the epidemic are considered suspected or probable COVID-19 cases, and the physicians performing the ECHO should take appropriate protective measures (wearing masks, gloves, helmets, etc.) to protect themselves and their patients.

The major cardiac involvement seen in adult patients with COVID-19 is acute myocardial injury (5, 8, 10-14). The shock is mostly seen as a part of multiorgan failure in critically ill patients in intensive care settings (11, 12). Another finding that observed in hospitalized and intensive care unit patients is arrhythmia (8, 10-12).

The results of the coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) study from Italy, in which the course of COVID-19 in pediatric emergencies was included, have been published (13). In this article, comparisons were performed with previously published pediatric studies. Generally, pediatric COVID-19, in patients younger than 18 years old, constitutes only approximately 1% of all COVID-19 patients. Clinical severity and hospitalization rates are also low, accounting for less than 11% of all pediatric cases. The mortality rate is also very low at 0 to 0.6%. In all pediatric studies, a fatal course was found to be associated with comorbidities in almost all patients. The most common cardiovascular finding was reported as tachycardia associated with fever. No case with direct myocardial injury or myocarditis as the first clinical finding has been reported (13).

Acute myocardial injury

Acute myocardial injury can develop in adults with 3 different mechanisms:

1) Severe pulmonary involvement, acute respiratory distress syndrome, or hypoxia/ischemia-induced multiorgan failure may lead to direct hypoxic myocardial injury. The reason for the elevated cardiac enzyme levels is usually acute hypoxic injury, especially in intensive care patients with poor prognostic criteria (8, 10-13).

2) Cytokine storm, which develops because of the systemic inflammatory response that may occur in the course of COVID-19 infection, may also cause myocardial injury (8, 15).

3) As seen in other coronaviruses (Middle East respiratory syndrome, severe acute respiratory syndrome), it has been shown in case reports that acute myocarditis can develop in the course of COVID-19 infection (8, 16-19). In rare case reports, myocarditis findings were shown in cardiac magnetic resonance imaging, and viral RNA and mononuclear cell infiltration of myocytes were demonstrated at autopsy (17, 18). It is thought that acute myocarditis may occur, particularly in patients with high viral load.

Acute myocyte damage (hypoxic or myocarditis) can progress asymptotically or lead to varying degrees of heart failure or rhythm disturbances. Patients with severe pulmonary

involvement and acute respiratory distress syndrome may also develop right heart failure and pulmonary hypertension. The treatment of choice in these patients is the standard heart failure treatment.

There have been no publications reporting definite primary cardiac involvement in pediatric patients. However, recently, a multisystem inflammatory syndrome similar to Kawasaki disease, toxic shock syndromes, and macrophage activation syndrome has begun to be identified, especially in reports from the United Kingdom (20). Myocarditis, valvulitis, pericardial effusion, and coronary artery dilatation have been reported in the cardiological evaluation of these patients. The SARS-CoV-2 polymerase chain reaction tests may be either positive or negative. Nevertheless, it has been emphasized that the frequency of this syndrome increases with COVID-19, emphasizing that early diagnosis is important and that immunomodulatory therapy should be planned with specific subspecialist consultations (e.g., rheumatology, immunology, and hematology) according to the clinical course (20). A very recent multicenter retrospective study from France and Switzerland reported on 35 children with multisystem inflammatory syndrome who presented with acute heart failure. Although the initial presentation may be severe, with some patients requiring mechanical respiratory and circulatory support, the authors observed rapid resolution of systolic dysfunction with the use of immune globulin and steroids. The authors proposed that the mechanism of heart failure is likely secondary to myocardial stunning or edema because of the rapid recovery and only mild to moderate elevation of troponin in their patient series (21). Pediatricians and pediatric cardiology specialists should be aware of this emerging syndrome, which is likely related to SARS-CoV-2 infection.

The approach to a possible case of myocarditis is the same as the treatment algorithms we use in other viral myocarditis. High dose intravenous immunoglobulin therapy may be beneficial in these patients owing to both antiviral and immunomodulatory efficacy of intravenous immunoglobulin (16).

In adult patients, although the underlying mechanism is not understood, the levels of the cardiac biomarkers c-troponin I/T and BNP/NT-proBNP increase concomitantly with the severity of the disease (10, 12, 15). This situation is generally interpreted as a result of hypoxic cardiac damage secondary to severe lung disease. Serial follow-up of these biomarkers is also used to

provide prognostic information in patients with a severe clinical course. Although there is not enough data regarding cardiac biomarkers in pediatric patients, it is appropriate to follow adult recommendations.

Arrhythmias

Sinus tachycardia owing to hypoxia and fever is frequently seen in the course of the disease. In addition, metabolic alterations, hypoxia, and inflammatory stress may cause development of arrhythmia, especially in intensive care unit patients. A wide range of arrhythmias may occur as a side effect of drugs used in the treatment of COVID-19 (8, 21, 22). Antiviral agents used in COVID-19 treatment, including hydroxychloroquine and azithromycin, are drugs with pro-arrhythmic effects (8, 10, 22, 23). QT and PR intervals have been shown to be prolonged after lopinavir/ritonavir use, especially in patients with a predisposing factor (8). It is known that lopinavir/ritonavir and ribavirin may affect the serum anticoagulant levels (8, 10). Azithromycin, which is frequently recommended in pediatric patients, may lead to QT prolongation, especially in at-risk patients (8).

It is also known that the hydroxychloroquine recommended in pediatric COVID-19 treatment may lead to prolongation of QT interval as a side effect (8, 22, 23). Close monitoring should be considered during the initiation and follow-up of these drugs, as they may lead to QT prolongation (7, 10).

QT interval follow-up protocol in the treatment of COVID-19

Before initiation of the treatment with QT prolonging agents, such as hydroxychloroquine and azithromycin, each patient should be evaluated individually and investigated for underlying risk factors (Table 1). ECG and QT monitoring should be performed once a patient is placed on treatment and during follow-up. Whether the patient will be hospitalized or followed as an outpatient has an effect on the initial treatment protocol and follow-up. QT measurement and monitoring should be done in the same lead (preferably D2 or V5).

QT monitoring protocol for inpatients

- Discontinue other potential QT prolonging medications or change to a drug with a lower risk of QTc prolongation.
- Perform baseline ECG, liver-kidney function tests, check serum potassium-magnesium level.

Table 1. Risk factors in patients who will use drugs prolonging QT

Risk factors

- Presence of congenital long QT syndrome
- Concomitant use of QTc prolonging medication for another reason
- Hypokalemia/Hypomagnesemia
- Accompanying heart disease (arrhythmia, cardiomyopathy, or heart failure)
- Baseline corrected QT (QTc) \geq 450 ms

- Keep serum K and Mg levels at “high–normal” levels. In this respect, patients using diuretics should be followed with great caution.
- Corrected QT (QTc) measurement should be done by using the Bazett formula.
- Relative contraindications include:
 - QTc greater than 500 ms (if QRS interval is greater than 120 ms, the QTc is greater than 530 to 550 ms)
 - Patients with congenital long QT syndrome

QT monitoring of hospitalized patients

- Check serum potassium level daily
- Perform ECG 2 to 3 hours after the second dose of hydroxychloroquine, followed by ECG once a day.
- If the QT interval is prolonged during follow-up, (QTc greater than 500 ms (if the QRS interval is greater than 120 ms, the QTc is greater than 530–550 ms) or if the QTc is prolonged more than 60 ms after initiation of treatment, change to a dose reduction protocol. If azithromycin was used, it should be discontinued and/or the hydroxychloroquine dose is reduced, daily ECG surveillance continues.
- If the QTc prolongation continues over 60 ms and/or QTc is greater than 500 ms (if the QRS interval is greater than 120 ms, the QTc is greater than 530 to 550 ms), the benefit of the treatment should be balanced against the increased risk and hydroxychloroquine should preferably be discontinued.

QT monitoring at outpatient clinics

- Discontinue other potential QT prolonging medications or change to a drug with a lower risk of QTc prolongation.
- Perform baseline ECG, liver-kidney function tests, and check serum potassium-magnesium level.
- Keep serum K and Mg levels at “high–normal” levels. In this respect, patients using diuretics should be followed with great caution.
- QTc measurement should be done by using the Bazett formula.
- In the case of kidney or liver impairment, QT prolonging medication should not be started.
- Relative contraindications include:
 - Patients with congenital long QT syndrome or
 - QTc greater than 480 ms (if the QRS interval is greater than 120 ms, the QTc is greater than 510 to 530 ms)
- Patients with risk factor are not monitored as outpatients.

Monitoring of outpatients who started medicine

- ECG monitoring is not required in patients with a low risk during quarantine and isolation.
- For at-risk patients, an ECG is taken 2 to 3 hours after the drug on the third day of medication. The drug is discontinued if the QTc is greater than 500 ms (if the QRS interval is greater than 120 ms, the QTc is greater than 530 to 550 ms) or if the QTc is prolonged more than 40 to 60 ms after the initiation of

treatment. In patients with QTc values between 460 and 500 ms, ECG surveillance is recommended.

Hydroxychloroquine may cause myocardial injury with long-term use, but it is not expected in these patients because of the short duration of treatment (24). Hydroxychloroquine can increase the serum level of beta-blockers (25). Patients on beta-blockers should be carefully evaluated and dose adjustments should be made when necessary.

Part B: COVID-19 infection in children with cardiac disease

The risk of children with cardiac disease for COVID-19 infection is not increased compared with their healthy peers. Similarly, there is no evidence-based data that clinical features will be more severe in children with heart disease if they experience COVID-19. On the other hand, the rates of morbidity and mortality of viral pulmonary infections in children with heart or lung disease is higher than among their healthy counterparts (2, 13, 26). Because the new coronavirus infection causes mostly pulmonary involvement, it is predicted that children with hemodynamically significant congenital or acquired heart disease may experience this infection more severely than healthy children. Based on this assumption, it is thought that the course of COVID-19 may pose a risk to children in the following disease groups (26):

- Patients either with single ventricular physiology or bidirectional cavopulmonary connection or Fontan palliation
- Patients with congenital heart diseases requiring surgery or transcatheter intervention under 1 year of age
- Patients with cyanotic congenital heart diseases whose oxygen saturation is consistently less than 85%
- Patients with pulmonary hypertension requiring treatment
- Patients with cardiomyopathy and heart failure requiring treatment
- Congenital heart disease patients with concomitant systemic diseases (e.g., chronic kidney disease, chronic lung disease)
- Patients using medication to improve heart function, with or without congenital heart disease
- Cardiac transplantation patients and those with ventricular-assist devices
- Patients with a hereditary disease commonly associated with immune system disorder (e.g., Down syndrome, Di-George syndrome, right atrial isomerism)

Parents should be informed to increase awareness of infection prevention in this group of patients. In addition, infected children should be followed closely and hospitalized earlier when needed. The requirement for hospitalization and intensive care resulting from COVID-19 infection in healthy children younger than 1 year of age is more common (27). For this reason, management of babies with a heart disease, especially those younger than 1 year old, is of particular importance. The urgency and importance ranking of diagnostic and interventional procedures should also be evaluated in infants with congenital heart disease

in this age group (28). Protection and treatment recommendations for children with heart disease who are not in this group are similar to their healthy counterparts.

It is known that the COVID-19 virus demonstrates penetration into tissues (e.g., heart, lung) with high expression of angiotensin converting enzyme 2 (ACE2) (8, 10, 12, 14). Therefore, controversy has intensified regarding patients using ACE inhibitors or angiotensin receptor blockers (ARB) that ACE2 expression may increase in tissue and increase viral damage in this way, but there is no consensus on the discontinuation of drugs. To date, it is recommended that adult patients using these group of drugs should continue their medication. In children, ACE inhibitors and ARB are both widely used for certain indications (e.g., hypertension, heart failure, valve failure, etc.). In the current literature, there is either no evidence-based data or there are low levels of evidence showing that ACE inhibitors and ARB use may worsen the COVID-19 clinical findings or improve the poor prognosis (10, 29). Considering the current data, the Turkish Pediatric Cardiology and Cardiac Surgery Association recommends that patients on any ACE inhibitor or ARB continue their medication according to current guidelines.

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