

Covid -19 Infection and Cardiac Complications in Children

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is the current pandemic disease causing severe disease and sometime life-threatening complications mainly in adults but also in children and young adults. Underlying diseases predispose the patients to a more severe disease and to a higher mortality rate. However, little evidence exists about COVID-19 outcomes in the pediatric population with congenital heart disease (CHD).

Aim: To summarize the current knowledge about the potential cardiovascular involvement in pediatric patients affected by COVID 19 with and without CHD, as well as some considerations for anti COVID vaccine.

Keywords: COVID-19, children, congenital heart disease

INTRODUCTION

Since 2019 the COVID-19 infection spread rapidly all over the world becoming a pandemic infection. The clinical spectrum of COVID-19 ranges from asymptomatic infection to mild respiratory tract symptoms to severe pneumonia with acute respiratory distress syndrome and multi-organ dysfunction. In children, COVID-19 infection appeared to be less aggressive as compared to adults. This might be due to the reduced number of receptors in their cells for the virus to attach in, or because the immune response in children is less expressed than in adults. Based on data reported to CDC (1), children with Covid 19 infection aged 0-17 years old counted 17.3% of total cases with Covid 19 infection in USA and mortality rate among this age group was about 0.1%. For the age group 18-29 years old there was a slightly increase in percentage up to 21.3% and the mortality rate increased up to 0.8%. Mostly, children present with symptoms such as fever, cough, shortness of breath, myalgia, rhinorrhea, sore throat, headache, nausea/vomiting, abdominal pain or diarrhea. The main serious complication in children affected by the disease is multisystem inflammatory syndrome (MIS-C) (2). In children who have a known history of documented or suspected COVID-19, the usual duration between acute infection and onset of MIS-C symptoms is two to six weeks. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious condition associated with COVID-19 (3). This complication is thought to be a consequence

of excessive release of cytokines or deregulation of T cells generated by the presence of the virus, resulting in microvascular damage and endothelial dysfunction (4). Patients with SARS-Cov-2-associated multisystem inflammatory syndrome frequently presented with persistent fever, gastrointestinal symptoms, polymorphic rash, conjunctivitis, and mucosal changes. Children presenting with MIS-C have demonstrated cardiac abnormalities by echocardiogram or laboratory parameters, including coronary artery aneurysms as seen in Kawasaki disease (5,6,7). MIS-C can cause in some children severe myocardial involvement requiring prolonged follow up over time (4).

About half of cases with MIS-C present with (Figure 1):

- Myocarditis (up to 19%)
- Dilation of coronary arteries (12-21%)
- Reduction of left ventricular function (28-55%)
- Pleural effusion (23%)
- Less commonly arrhythmias (5-8)

Cardiovascular Implications Associated with SARS-CoV-2

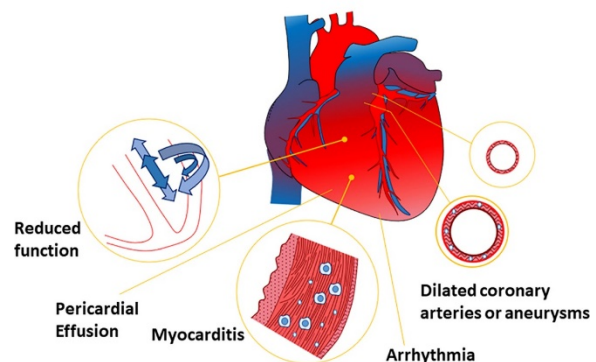


Figure 1. Cardiovascular implications associated with SARS-COV-2 infection (8)

Usually MIS-C symptoms resolve within 1-4 weeks (8) after establishing diagnosis with a mortality rate 1.4-1.9%. Mechanism of cardiac injury in COVID-19 and its effects on the cardiovascular system are not fully understood. In some studies, cardiac injury (manifested as an increase in troponin levels) was found in admitted patients and cardiac injury was more common in critically-ill patients.

Mechanisms of cardiac injury in covid-19

Mechanism of cardiac injury in COVID-19 and its effects on the cardiovascular system are not fully understood. In some studies, cardiac injury was found in admitted patients and cardiac injury was more common in critically-ill patients. Several mechanisms have been proposed (3,9):

- COVID-19 may cause cardiac injury indirectly due to an overwhelming immune inflammatory response and cytokine storm.
- SARS-CoV-2 viral invasion of cardiomyocytes and direct damage via this process, but this has not been proven.
- Severe hypoxia from acute respiratory damage caused by the virus may result in oxidative stress and myocardial injury from increased myocardial oxygen demand in the presence of severe hypoxia due to acute lung injury (ARDS).
- Furthermore, ACE2 is expressed in the heart, and the SARS-CoV-2 virus uses this enzyme as a receptor for entry into the cell. It is unclear whether SARS-CoV-2 binding alters ACE2 expression or causes

dysregulation of the RAAS (renin angiotensin-aldosterone system) pathway.

Cardiovascular manifestations:

Cardiovascular manifestations in COVID 19 infection, in children occur rarely and may include (9,10):

- *Myocarditis:* In a recent study published in the Morbidity and Mortality Weekly Report from the Centers for Disease Control (CDC), only 86 children <16 years of age were diagnosed with myocarditis among nearly 65,000 (0.133%) children with COVID-19. Acute myocardial injury by SARS-CoV-2 may be due to the coincidence of various mechanisms including a direct viral myocardial injury, a secondary inflammatory response in the form of cytokine storm, the severe hypoxemia due to pneumonia, and the side-effects of therapy against SARS-CoV-2 infection (9,11). Based on reports to the Chinese Center for Control and Prevention, myocardial injury or heart failure was found in 0.6% pediatric patients with Covid 19 infection (12). Based on the few published data, SARS-CoV-2 may represent a potential novel etiology of fulminant myocarditis, which should be suspected in COVID-19 patients with acute-onset chest pain, ST-segment changes, cardiac arrhythmias and hemodynamic instability (12,13,14). It

is suspected based on laboratory data as the elevation of cardiac enzymes like increase in troponin level and CK-MB level, ECG anomalies (ST-T wave changes) and MRI findings (presence of late gadolinium enhancement).

- *Pericarditis*: is a rare cardiac complication of COVID-19 infection. Cases reported of pericarditis in COVID 19 infection have occurred in the acute phase (15) of the disease or after complete recovery (16).
- *Arrhythmias*: There are little data about the occurrence of arrhythmias in the context of pediatric COVID-19. Data from 2 small-sized studies showed that hospitalized pediatric COVID-19 cases could present a rate of cardiac arrhythmia as high as 16%-20% (17,18). Children manifest less harmful rhythm trouble such as ventricular tachycardia (18,19), atrial tachycardia, AV block 1-st grade etc. Ventricular arrhythmias seem to be directly correlated to the COVID-19 induced myocardial injury. According to Samuel et al (17), 4 out of 5 cases of ventricular arrhythmia presented abnormal echocardiograms with mild dilation/dysfunction of the left ventricle (17). The major part of these arrhythmias haven't need any treatment and sometime anti arrhythmic drugs have been used.

Co-existence of myocardial injury and Covid 19 infection:

The coexistence of myocardial injury and cardiac arrhythmias with COVID-19 makes the diagnosis and management of this entity rather challenging. The early recognition of cardiac symptoms and their timely treatment may be of pivotal importance to improve the prognosis of pediatric patients, overall in those with severe disease (13). In children with COVID 19 infection suspected to have cardiovascular involvement, the diagnosis is made based on:

- Abnormal biomarkers: Increase level of troponin, NT-pro-BNP;
- ECG changes: ST level changes, myocardial ischemia, ventricular extra systoles, atrio-ventricular block etc.;
- Cardiac ultrasound:
 - ventricular dysfunction (left/right or both)
 - mitral regurgitation
 - pericardial effusion
 - z score \geq -2 of dilatation in one of proximal branches of coronary arteries.

As showed in the picture below (Figure 2) there is an algorithm to keep in mind in cases with suspected cardiovascular involvement. We suspect cardiac dysfunction when the child complain fatigue, drowsiness, shortened of breath etc. Then we have different steps to better evaluate cardiac involvement, like chest x Ray, chest Ct scan, troponin and cardiac enzymes, ECG and cardiac echo (19).

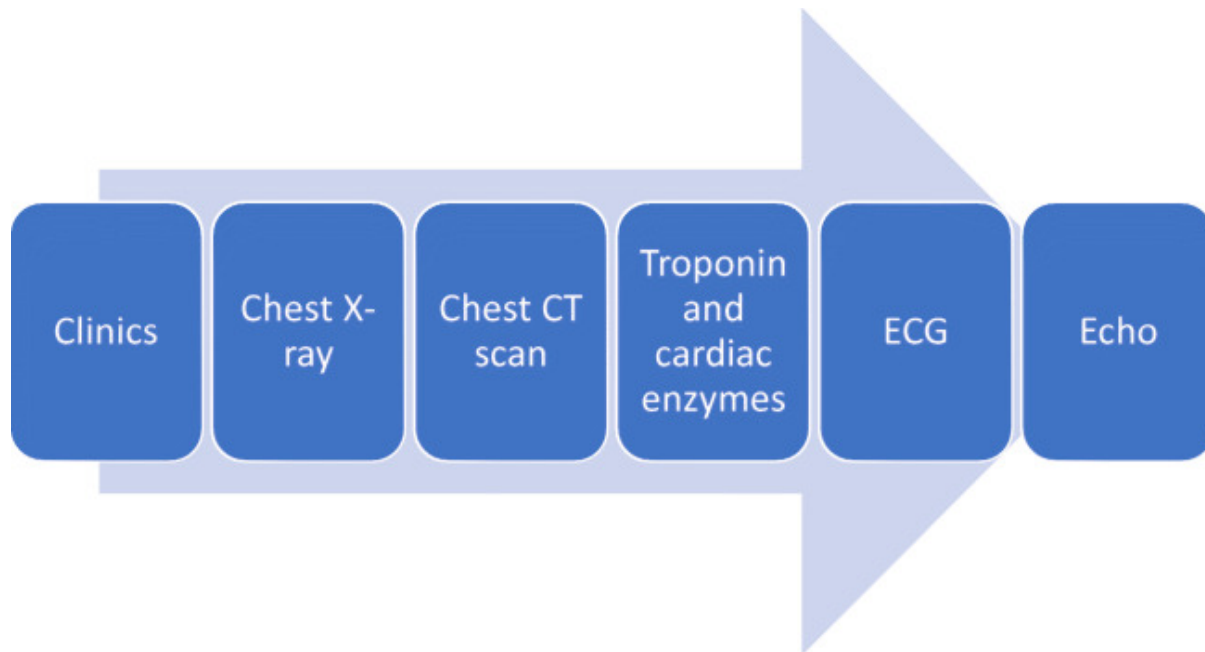


Figure 2. Diagnostic algorithm (19).

Different studies showed that children with a chronic disease are more prone to have a more severe infection compared to healthy children (20). Congenital heart diseases (CHD) affect approximately up to 8/1000 (0.8%) newborns and remain the leading cause of infant mortality due to congenital malformations (21). Currently there are few studies focusing on children with CHD and COVID 19 related morbidity and mortality, mainly case reports or small case series (13). These children seem to be a vulnerable population to a potential clinical deterioration in the presence of bilateral pneumonia or acute respiratory distress syndrome caused by SARS-CoV-2, especially those with non-corrected complex cardiac defects and decreased cardiopulmonary functional reserve (10,22).

It is important to recognize that there is a broad range of anatomical and physiological

abnormalities among patients with CHD, and it is likely that not all are at similar risk for severe disease. In general, patients with impaired ventricular function and those with abnormal pulmonary blood flow/ pulmonary hemodynamics are considered to be at higher risk (13,22,23). In some studies results are controversial regarding the risk of having severe COVID 19 infection in children with cardiac diseases.

A congenital cardiopathy is considered to have low risk for severe Covid 19 infection when (24):

- the child is asymptomatic;
- the heart has normal shape and dimension;
- the pump function isn't altered;
- the heart rhythm is normal;

- there is no pulmonary hypertension and the valvular anatomy is normal.

Based on the British Congenital Cardiac Association, children with cardiopathies are considered at increased risk of severe coronavirus illness if they have “hemodynamically significant” congenital heart disease, or milder congenital heart disease as well as another health condition (20,24).

The high risk category includes (24):

- Fontan circulation or single ventricle, such as tricuspid atresia or hypoplastic left heart syndrome.
- Children chronic cyanosis (oxygen saturations are consistently below 85%).
- Cardiomyopathy or cardiac failure.
- Children with CHD less than 1-year-old untreated which require cardiac surgery.
- Pulmonary hypertension under treatment.
- Children than had a heart transplant to treat their congenital heart condition.
- Children with cardiopathies and other medical problems such as lung disease or kidney disease.
- Children under treatment with drugs like immunosuppressant or high doses of steroids.
- Children with immunodeficiencies like Di George syndrome.

Studies related to children and adolescents with congenital cardiac diseases and the gravity of Covid 19 infection are controversial. Some of them report higher risk of life-threatening illness

and complications from COVID-19 (25). In one retrospective study conducted in USA, was shown that some previous or preexisting cardiovascular conditions including: cardiogenic shock, heart surgery, pulmonary hypertension, heart failure, hypotension, pericarditis, and biventricular defects, were associated with increased COVID-19 severity in US pediatric patients (25). Children with Down Syndrome and congenital heart diseases are also more prone to have severe infection and require intensive care management including ventilatory support especially those with cyanotic cardiopathies (3,26-28). Covid 19 infection can worsen the degree of hypoxia and compromises tissues perfusion. In other studies, it is shown that children with cardiac anomalies were not at high risk for encountering Covid 19 infection. For those children also was noted low gravity of infection and low mortality rate (3,29). Those studies showed:

- A similar rate of infection between children with idiopathic HAP and general pediatric patients.
- Similar mortality rate in children and adults with congenital heart disease.
- It does not appear that patients with congenital heart disease or a previous history of S. Kawasaki are at a higher risk for developing MIS-C.

During pandemic different questions emerged regarding therapies and vaccination.

Should we give maintenance therapy to children with congenital heart disease to support heart function during pandemic?

Concern exists about the potential risks of deleterious effects of these drugs when they are administered during SARS-CoV-2 infection (13).

- American Heart Association banned discontinuation of ACE-inhibitors and angiotensin type II receptors blockers ARB in cardiac patients suspected or positive for Covid 19 infection.
- None of the cardiac medications used in children with CHD have shown to worsen or to have any impact in case of Covid 19 infection in these group of patients.
- All medications used like aspirin, anticoagulants, ACE-inhibitors, ARB, diuretics and antiarrhythmic drugs should continue during the Covid infection, otherwise there is a clear contraindication.

Is there any treatment for MIS-C and myocardial infarction?

MIS-C and myocardial infarction are really severe life-threatening events during Covid 19 infection. Current practices and published guidelines for the treatment of MIS-C support the use of intravenous immunoglobulin (IVIG) and/or high-dose corticosteroids as a first-line of therapy to limit inflammation. (30).

Is there any implication of Covid 19 vaccines in heart function?

- For the majority of pediatric and adolescent patients the vaccine will have no effect on heart function, but in very rare cases was shown a relation between vaccination and development of myocarditis or pericarditis.
- Myocarditis was the main article as the severe complication of mRNA vaccines.
- Studies suggested that the risk for this complication after vaccination was low, in less than 1 case in 20000 vaccinated children of the age 12-17 years old, and even lower for others ages groups. Symptoms developed with 1-4 days after the second dose of injection (16 cases per 1 million vaccinations).
- In this contest is important to make clear that even though rare, Covid infection by itself can cause more cardiac inflammation than vaccine can do (31).

How serious is myocarditis and pericarditis after vaccine administration?

Most of children and adolescent with vaccine-associated myocarditis present mild symptoms such as chest pain and shortness of breath which stabilizes soon within few days after hospital admission and treatment (NSAID and IVIG). The time required for symptoms relieve is usually less than 3 days (32).

Which ages are more prone to develop myocarditis?

Studies revealed that this complication can occur at any age, but was more often seen in males aged 12-29 years old. Myocarditis incidence even in the high risk group, males aged 12-17 years old was 1 in 15000 vaccinated males (33).

Is there any contraindication to vaccine for children with congenital heart disease?

- It is important to say that congenital heart diseases are not a reason to avoid vaccination.
- It is strongly recommended vaccination for children suffering from a cardiac disease in order to protect them from encountering a Covid infection and its complications.
- For patients with recent cardiac surgery or patients under treatment with medications interfering in their immune system they can get their vaccine based on cardiologist advise.

Are children with congenital heart disease in increased risk for adverse or side effects vaccine related?

Children and young adults suffering from a cardiac disease are not in increased risk compare with healthy children of getting myocarditis due to their cardiac history. When they present myocarditis (for any reason) close follow up from their cardiologist is recommended (34).

What is known for vaccine associated myocarditis?

Vaccine associated myocarditis happens as a result of immune system dysregulation causing heart inflammation.

Myocarditis has more often an autoimmune mechanism triggered by a viral infection, is possible that in vaccine associated myocarditis the basis may be also an autoimmune reaction. Sars-Cov2 infects many cells even cardiac cells causing myocarditis. In a study was compared the incidence of myocarditis in COVID-19 vaccinated individuals and in severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection group of individuals. The study showed that myocarditis was found 7 time more often in the infected group compare to the vaccinated group (35).

How to suspect the child is having myocarditis?

If the child experience chest pain, arrhythmias, tachycardia, nausea, polypnea, after a confirmed Covid 19 infection or within 4-5 days after vaccine administration is important to seek medical evaluation.

How long after myocarditis should children wait to return to sports?

It is recommended for the child to gradually start doing sports after 3-6 months from diagnosis, in close supervision of their cardiologist if they have any symptoms or problems (36).

CONCLUSION

In children with congenital heart disease affected by Covid 19 infection, cardiovascular complications, severe forms and death are rare: more risked are children with complex cardiopathies.

The impact of Covid 19 infection and its complications like long Covid syndrome need to be elucidated in children and adolescent with or without cardiac diseases.

The risk for developing myocarditis is higher in case of Covid 19 infection compared to mRNA vaccination. Vaccination benefit exceeds the risk.

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