

Cardiovascular effects of COVID-19 in children

Meredith CG Broberg¹ MD, Monty B Mazer¹ MD, Ira M Cheifetz¹ MD

ABSTRACT

Introduction: Although severe acute respiratory failure is the primary cause of morbidity and mortality in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, this viral infection leads to cardiovascular disease in some individuals. Cardiac effects of the virus include myocarditis, pericarditis, arrhythmias, coronary aneurysms and cardiomyopathy, and can result in cardiogenic shock and multisystem organ failure.

Method: This review summarises cardiac manifestations of SARS-CoV-2 in the paediatric population. We performed a scoping review of cardiovascular disease associated with acute coronavirus disease 2019 (COVID-19) infection, multisystem inflammatory syndrome in children (MIS-C), and mRNA COVID-19 vaccines. Also examined are special considerations for paediatric athletes and return to play following COVID-19 infection.

Results: Children presenting with acute COVID-19 should be screened for cardiac dysfunction and a thorough history should be obtained. Further cardiovascular evaluation should be considered following any signs/symptoms of arrhythmias, low cardiac output, and/or myopericarditis. Patients admitted with severe acute COVID-19 should be monitored with continuous cardiac monitoring. Laboratory testing, as clinically indicated, includes tests for troponin and B-type natriuretic peptide or N-terminal pro-brain natriuretic peptide. Echocardiography with strain evaluation and/or cardiac magnetic resonance imaging should be considered to evaluate diastolic and systolic dysfunction, coronary anatomy, the pericardium and the myocardium. For patients with MIS-C, combination therapy with intravenous immunoglobulin and glucocorticoid therapy is safe and potentially disease altering. Treatment of MIS-C targets the hyperimmune response. Supportive care, including mechanical support, is needed in some cases.

Conclusion: Cardiovascular disease is a striking feature of SARS-CoV-2 infection. Most infants, children and adolescents with COVID-19 cardiac disease fully recover with no lasting cardiac dysfunction. However, long-term studies and further research are needed to assess cardiovascular risk with variants of SARS-CoV-2 and to understand the pathophysiology of cardiac dysfunction with COVID-19.

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Keywords: arrhythmia, COVID-19, myocardium, paediatric, SARS-CoV-2, ventricular dysfunction

CLINICAL IMPACT

What is New

- Cardiovascular disease is a striking feature of SARS-CoV-2 infection, and can manifest during acute and post-infection and following mRNA vaccination.
- The hypothesised mechanism of cardiomyocyte injury includes direct viral invasion by SARS-CoV-2 leading to direct cellular damage with subsequent leukocyte recruitment and immune-inflammatory process.

Clinical Implications

- Children presenting with acute COVID-19 should be screened for cardiac dysfunction and a thorough history should be obtained.
- Further cardiovascular evaluation should be considered following any signs/symptoms of arrhythmias, low cardiac output, and/or myopericarditis.

INTRODUCTION

The global coronavirus disease 2019 (COVID-19) pandemic was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While the respiratory system is the primary infectious target of SARS-CoV-2, systemic symptoms are fairly common and organ systems throughout the body can be affected with multisystem organ failure in the most severe cases.¹ Cardiovascular involvement, including thrombosis, infarction, dysfunction and arrhythmia are present in varying degrees of severity and prevalence in the adult and paediatric populations. Paediatric cardiac manifestations of COVID-19 are exceptionally important to the evaluation and management of children with both mild and severe COVID-19 infection.²⁻⁴ This review focuses on the various cardiac pathologies, clinical presentations, evaluations and recommended follow-up for the paediatric cardiac manifestations of COVID-19 infection.

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¹ Division of Cardiac Critical Care, UH Rainbow Babies & Children's Hospital, Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, Ohio, United States
Correspondence: Dr Meredith CG Broberg, UH Rainbow Babies and Children's Hospital, 11100 Euclid Ave, Mail Stop 6011, Cleveland, OH 44106, United States.
Email: Meredith.Broberg@UHhospitals.org

METHOD

We performed a scoping review by searching Scopus and PubMed/MEDLINE using the keywords/phrases: "COVID 19", "coronavirus", "COVID-19/ complications", "SARS-CoV-2", "pediatric multisystem inflammatory disease, COVID-19 related", (AND) "cardiovascular diseases", "arrhythmias", "myocardial infarction", "myocarditis", "sports", "vaccine", "thrombosis" with a paediatric, infant and adolescent filter. Abstracts and reference lists were individually examined by one author (MCGB) to retrieve articles focused on cardiovascular disease associated with COVID-19 in the pediatric population. Only articles written in English were considered. Case reports, observational studies, systematic reviews, meta-analysis, basic science and translation studies, and prospective trials were included in this review.

RESULTS

Cardiovascular disease in COVID-19

Cardiovascular disease associated with COVID-19 is now well described,⁵ with 20–62% of adults hospitalised with COVID-19 diagnosed with a newly developed cardiovascular condition leading to increased morbidity and mortality.^{3,4,6} The prevalence of COVID-19-associated cardiovascular disease in the paediatric population is difficult to estimate due to a high proportion of mild COVID-19 and asymptomatic infections not evaluated for cardiac disease. However, a prevalence of up to 11.2% cardiac involvement in symptomatic infections in children has been estimated.⁷ Cardiovascular manifestations include myocardial dysfunction, pancarditis (pericarditis, myocarditis, valve disease and coronary disease) and arrhythmias. Cardiac involvement is thought to be caused by direct infection and/or systemic inflammation of hypercoagulability.

There are undoubtedly several mechanisms of injury in COVID-19 leading to cardiac dysfunction. The target of SARS-CoV-2 for cellular internalisation is the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 converts angiotensin-II to angiotensin-(1–7), which has vasodilatory properties and acts as counter regulator of the renin-angiotensin system and controls excessive inflammation by reducing circulating angiotensin-II—a pro-inflammatory enzyme and pro-oxidant during stress. Loss of ACE2 function increases susceptibility to heart failure. The hypothesised mechanism of cardiomyocyte injury includes direct invasion by SARS-CoV-2 leading to direct cellular damage with subsequent leukocyte recruitment and immune-inflammatory process. Viveiros et al. demonstrated ACE2 downregulation at days 7 and 14 of

SARS-CoV-2 infection in animal models infected with ancestral SARS-CoV-2.⁸ This downregulation was not seen in animals infected with the Delta variant. The authors hypothesised that the persistence of myocardial ACE2 may be protective and may be an explanation for the variation in cardiovascular disease severity among different viral strains. It is speculated that the virus also has direct effects on the sinus node by increasing ACE2 expression,⁹ and this effect abates as the viral load decreases. Furthermore, the virus leads to cytokine storm and severe inflammation resulting in myocarditis with cardiomyopathy and/or dysrhythmia.

Autopsy reports demonstrate upregulation of oxidative stress-induced apoptosis in pericytes, upregulation of cell adhesion and immune pathways in cardiomyocytes, and changes to cell differentiation processes in fibroblasts.¹⁰ Additional autopsy studies from COVID-19 non-survivors revealed varying degrees of neutrophil and lymphocyte infiltration of myocardial tissue. Acute ischaemia and necrosis were noted in a small number of deceased subjects. Oprinca et al. demonstrated positive SARS-CoV-2 antigen within the myocardium in 2 of 16 patients evaluated,¹¹ similar to the study by Zhang et al.¹² Autopsy reports of paediatric patients with SARS-CoV-2 infection revealed pancarditis with diffuse inflammatory infiltrate of lymphocytes, macrophages, eosinophils, focal myocyte necrosis interstitial oedema, and coronary artery abnormalities including diffuse coronary artery ectasia.^{13,14}

Acute paediatric COVID-19 and cardiac implications

Infants, children and adolescents are mostly asymptomatic or develop mild respiratory symptoms when infected with SARS-CoV-2. The prevalence of severe disease is difficult to determine as the vast majority of paediatric patients do not seek medical care. Early epidemiology studies report 0.6–3% of children^{15–17} develop multisystem organ failure, cardiovascular compromise, and shock. Underlying cardiac disease, either congenital heart disease or pre-existing cardiomyopathy, increases the risk of severe disease.^{15,18,19}

Arrhythmias

The manifestation of arrhythmias in an acute COVID-19 infection is likely due to multiple mechanisms, including increased right ventricular (RV) afterload and myocardial strain, electrolyte disturbances, hypoxia, medications, inflammation and myocardial ischaemia.²⁰ Reported arrhythmias include bradyarrhythmias (from transient severe sinus bradycardia to high degree heart block), tachyarrhythmias (including supraventricular

tachycardia, monomorphic ventricular tachycardia [VT]), and polymorphic VT.^{20,21} Patients with inherited arrhythmia disorders may have increased risk of arrhythmias with SARS-CoV-2 infection.²⁰ Notably, relative bradycardia in adults with acute COVID-19 is common,⁹ independent of myocardial injury and resolves during convalescence. This has also been reported in a 14-year-old without other manifestations of cardiac disease. Bradycardia resolution coincided with the SARS CoV-2 polymerase chain reaction (PCR) test returning negative.²²

In a multicentre cohort analysis of 3600 hospitalised paediatric patients with acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C), tachyarrhythmia occurred in 1.8% of patients admitted with acute severe COVID-19 infection and 1.7% with MIS-C.²³ MIS-C is described in more detail below. Tachyarrhythmias including supraventricular tachycardia (most commonly ectopic atrial tachycardia) and ventricular arrhythmias (including VT and/or ventricular fibrillation) were seen more frequently in patients with acute cardiac involvement (coronary dilatation [z-score ≥ 2.5], pericarditis, pericardial effusion, elevated B-type natriuretic peptide [BNP], elevated troponin, or ventricular dysfunction), older patients, and patients with a higher severity of illness. Tachyarrhythmias were more likely to occur in patients with acute COVID-19 who had underlying cardiovascular comorbid conditions. The association between comorbidities and tachyarrhythmias was not seen in patients with MIS-C. Several patients with arrhythmias required interventions including antiarrhythmic medications (49%), electrical conversion (17%), cardiopulmonary resuscitation (13%), and/or extracorporeal support (14%). Tachyarrhythmia is associated with a longer length of hospital stay and death.²³

Cardiac dysfunction

Systemic infection, severe hypoxia, sepsis and direct myocarditis are mechanisms of cardiomyopathy in acute paediatric COVID-19.²⁴ However, cardiac dysfunction associated with COVID-19 in children is more commonly post-infectious, mediated by systemic inflammation—a syndrome now referred to as MIS-C. One of the first reported paediatric cases of severe cardiac dysfunction with complete atrioventricular block (AVB) occurred in a 12-year-old girl who presented to care on day 3 of symptoms with fever, abdominal pain and cyanosis with positive SARS-CoV-2 and adenovirus test results. She rapidly improved following administration of intravenous immunoglobulin (IVIG).²⁵ There is now a substantial body of evidence reporting a rare incidence of acute myocarditis associated with positive viral PCR test result;^{26–30} however, it is retrospectively difficult

to determine whether cardiac dysfunction occurred during acute disease or following the acute illness as a result of post-infectious immune dysregulation. Regardless, the adjusted myocarditis risk ratio is 36.8 for patients less than 16 years admitted to the hospital with COVID-19.³¹

Acute coronary syndrome has also been reported to occur with acute COVID-19 infection in paediatric patients. A study reported an adolescent who presented with an acute ST-elevation myocardial infarction with thrombus in the distal ramus branch of the left coronary artery and the distal left anterior descending coronary artery.³² Percutaneous intervention was not performed due to time to catheterisation and clot location, though she was treated with remdesivir. Hypercoagulation evaluation was unrevealing, and unlike patients with MIS-C, nonspecific inflammatory markers were not elevated. She subsequently developed left ventricular (LV) thrombi in the setting of apical akinesis and anticoagulation noncompliance.

Multisystem inflammatory syndrome in children

Early in the pandemic, clinicians in Europe reported increased incidence of Kawasaki-like illness. However, it occurred in older children (6–12 years) and had a higher rate of myocardial involvement.³³ Initially named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), it is now referred to as MIS-C. Although the pathophysiology leading to MIS-C is debated, there are several likely overlapping hypotheses involving dysregulated activation of the immune system with proinflammatory cytokine production, autoantibodies and immune cellular tissue infiltration leading to endothelial dysfunction, myocardial injury, capillary leak, and a hypercoagulable state.^{34–36} There are additional reports of autopsy and biopsy studies in severe or fatal MIS-C demonstrating viral infiltration of myocardial tissue.³⁷ Most common clinical symptoms include fever, rash and gastrointestinal symptoms.^{38–40} The majority of cases (53–83%) were found to have cardiac involvement,^{33,39,41,42} with hyperinflammatory disease leading to pancarditis with LV dysfunction and coronary disease. Consequently, patients experience arrhythmias, repolarisation abnormalities, and conduction delays as well as cardiovascular collapse requiring intensive care, inotropes and extracorporeal life support.^{40,41,43–45}

The World Health Organization (WHO), Royal College of Paediatrics and Child Health and Centers for Disease Control and Prevention developed similar case definitions to aid in the diagnosis of MIS-C. The WHO uses 6 diagnostic criteria, all which must be met for diagnosis: (1) age 0–19 years, (2) fever for 3 or more days, (3) clinical

signs of multisystem involvement, (4) elevated markers of inflammation, (5) no other obvious microbial cause of inflammation, and (6) evidence of SARS-CoV-2 infection.⁴⁶ Signs of multisystem involvement include rash, bilateral non-purulent conjunctivitis, mucocutaneous inflammation, hypotension, cardiac dysfunction, pericarditis, valvulitis, coronary abnormalities, coagulopathy, or acute gastrointestinal symptoms. Laboratory investigation yields elevated C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, ferritin, lactate dehydrogenase, fibrinogen, D-dimer, interleukin-6 (IL-6). Other lab abnormalities include neutrophilia, lymphopaenia, hypoalbuminaemia.⁴⁷ Several patients, especially those with haemodynamic instability, have elevated troponin and BNP.⁴⁸

Compared with typical Kawasaki disease, patients during the SARS-CoV-2 epidemic were older, less likely to present with coronary abnormalities (13.2% versus 28.1%, $P=0.043$, respectively), and had a higher incidence of myocarditis, pericarditis, valvular insufficiency, heart failure and shock.⁴⁵ Unlike Kawasaki disease, cardiac-associated autoantibodies have been found in circulation including against P2RX4, ECE1, MMP14, PDL1M5 and EIF1AY.^{49,50} Coronary disease is reported in 8–24% of patients with MIS-C.⁴⁴

Approximately 70% of patients with MIS-C have electrocardiogram (ECG) changes, including low QRS amplitudes and transient T-wave inversion in the anterior leads.⁵¹ Arrhythmia prevalence is reported to range from 1.8–21%^{23,51} and portend a more severe course.²³ Haghighi Aski et al. meta-analysed 21 studies with 916 children and found a pooled prevalence of 28.1% for ECG abnormalities or cardiac arrhythmias, including ST-segment changes, QT interval prolongation, sinus bradycardia, AVB, junctional cardiac rhythm, supraventricular tachycardia, and ventricular arrhythmias.⁴³

LV dysfunction is common with a pooled prevalence of 38%, with both global dysfunction and regional wall motion abnormalities described.⁴³ Troponin, BNP and CRP levels correlate with ventricular dysfunction severity.^{38,52} Mild or moderate atrioventricular (AV) regurgitation is seen in 10–72% of patients.^{53,54} Global circumferential strain, peak left atrial strain, and peak longitudinal strain of the RV free wall are predictive of myocardial injury.⁵⁵ The majority of patients with LV dysfunction recover within 30 days;⁵⁶ however, diastolic dysfunction may persist.⁵⁵ Cardiac magnetic resonance imaging (MRI) performed during acute illness on 3 patients revealed myocardial oedema but no evidence of scar or fibrosis.⁵⁷ At 2-month follow-up, cardiac MRI findings were completely resolved.⁵⁸

Treatment for MIS-C targets the immune-mediated hyperinflammatory state. First-line treatment for hospitalised patients includes glucocorticosteroids and IVIG.^{47,59–61} Immunomodulators, such as IL-1, tumour necrosis factor alpha and IL-6 antagonists have been attempted for refractory disease. Some children are reported to improve with supportive treatment alone;^{62,63} however, due to the concern that hyperinflammation can worsen cardiac dysfunction and coronary aneurysms without intervention, combination therapy is recommended.⁶⁴ To our knowledge, in the only randomised, open-label study comparing intravenous methylprednisolone to IVIG in patients with MIS-C, there was no difference in length of stay, cardiac events, need for inotropes, intensive care admission and renal replacement therapy.⁶⁵ However, approximately 30% of participants in this study received additional anti-inflammatory therapy including the other study drug.⁶⁵ The largest observational study to our knowledge, showed no difference in disease severity and need for mechanical support or inotropes on day 2 of illness with either IVIG alone, glucocorticosteroids alone, or both IVIG and glucocorticosteroids.⁵⁹ Patients treated with both IVIG and glucocorticoids were less likely to require escalation to an additional immunomodulator therapy. In other studies, patients receiving monotherapy with IVIG were more likely to fail treatment, develop new cardiac dysfunction and require longer intensive care unit (ICU) care, compared to IVIG plus glucocorticosteroids.^{60,61} Patients with evidence of coronary abnormalities were treated with antiplatelets and anticoagulation, depending on the severity of coronary disease.⁶³ Treatment for MIS-C should be conducted with a multidisciplinary approach in consultation with cardiologists, infectious disease specialists and/or rheumatologists.

The majority of patients with cardiac disease due to MIS-C have complete recovery. Over 90% of patients with reduced LV function and 79% of patients with coronary artery aneurysms normalised by 30 days.⁵⁶ A study of 28 patients with MIS-C in Nigeria showed complete normalisation of all patients' echocardiogram and ECG at 6-month follow-up.⁶⁶ In a study of 45 children with MIS-C in the US, only 1 child at 9 months had mild ventricular dysfunction and 1 child had mild residual AV regurgitation.⁶⁷ Mortality in high-income countries has been reported to be low (<2%), but higher in middle-income countries at 9–15%.^{68–71} Mortality is associated with high ferritin levels and cardiovascular complications.⁶⁸

Vaccine-induced cardiomyopathy

In December 2020, an Emergency Use Authorization was issued for emergency use of COVID-19 vaccine in the US for individuals 16 years and older. By May 2021, it was available for ages 12–15 years. As billions of people began to be vaccinated globally, safety events that had not been demonstrated in clinical trials were detected.^{72,73} Most notably, cases of vaccine-associated myocarditis and/or pericarditis were reported in young males after receiving an mRNA vaccine. Reports from the US,^{74,75} UK,^{76,77} Israel,^{73,78} Canada⁷⁹ and Nordic countries⁸⁰ described an increased incidence of myocarditis/pericarditis, with adolescent and young adult males being at highest risk following the second vaccine dose. The incidence of myocarditis after 2 mRNA vaccine doses is highest in male adolescents (12–17 years) with a case range of 50–139 per million and in male young adults (18–29 years) with a case range of 28–147 per million.⁸¹ The mRNA-1273 vaccine had a greater risk of myocarditis/pericarditis than following dosing with BNT162b2 vaccine.^{76,77,79,80} In the UK,^{76,77} increased risk of myocarditis occurred after the second dose of the BNT162b2 mRNA vaccine in the age group 16–29 years (incident rate ratio [IRR] 2.88, 95% confidence interval [CI] 1.24–6.72) and more pronounced after the second dose of the mRNA-1273 vaccine (IRR 74.39, 95% CI 5.28–1048.75). According to these studies by Patone et al., the IRR for myocarditis in persons less than 40 years of age was greater following the second dose of the mRNA-1273 vaccine (IRR 20.71, 95% CI 4.02–106.68) than after a positive SARS-CoV-2 test prior to vaccination (4.06, 95% CI 2.21–7.45).^{76,77}

Most cases of myocarditis/pericarditis present within 7 days of the vaccine, usually on day 2 or 3,^{73,74} with chest pain, dyspnoea, and palpitations.^{74,81} Troponin elevation has been ubiquitous in cases, and the majority of patients demonstrate ECG abnormalities.^{74,75,81} The American paediatric experience detailing cases from 26 centres and 139 patients found 70% of patients had an abnormal ECG.⁷⁵ All but 2 patients with an abnormal ECG had ST or T-wave changes/elevation. Seven patients had non-sustained VT.⁷⁵ The minority of patients had LV dysfunction (14–29% across studies).⁸¹ Most cases of vaccine-associated myocarditis/pericarditis have been mild.^{75,78,80,81} While the majority of cases in the US were hospitalised, very few required vasoactive/inotropic medications and/or mechanical support.⁷⁴ Nonsteroidal anti-inflammatory medications were the most common therapeutics. Rare deaths have been reported with 1 fatality reported in Israel for a 22-year-old with fulminant myocarditis,^{78,81}

and 84 fatalities among 5611 cases (1.5%) reported in the unconfirmed series from the EudraVigilance data—causes of deaths were not reported.⁸¹ Most patients recover completely with only a few showing abnormalities on follow-up cardiac MRI or echocardiogram at 3 months.^{75,81}

Numerous mechanisms have been proposed to explain mRNA vaccine-associated myocarditis/pericarditis, such as hyperimmune or inflammatory response, autoimmunity triggered by molecular mimicry, delayed hypersensitivity (serum sickness), eosinophilic myocarditis, and hypersensitivity to the vaccine vehicle components.⁸¹ Autopsy reports from 2 adolescent boys, who died on days 3 and 4 following their second dose of the BNT162b2 mRNA vaccine were not consistent with typical myocarditis findings and demonstrated an injury pattern similar to takotsubo or stress-induced cardiomyopathy. The authors propose this may represent an overly exuberant immune response with the myocardial injury mediated by similar cytokine storm seen in MIS-C and catecholamine feedback loop.⁸² In 2 other autopsy series of adult patients—the first with 15 patients between ages 18–68 years who died in-hospital with cardiac disease following vaccination⁸³ and the second with 25 individuals between ages 46–75 years who died unexpectedly at home within 20 days of a COVID-19 vaccination—histologic findings showed a lymphocyte predominant epi-myocarditis consistent with an autoimmune myocarditis.⁸⁴ These series suggest that the possibility of molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens may trigger an immune response in some individuals leading to myocarditis; however, the exact mechanism remains unknown.⁸²

Athletes

As patients with COVID-19 presented with cardiovascular disease, specifically myocarditis, concern arose surrounding the possibility of developing asymptomatic or undetected cardiac disease post-infection with regards to the safety of athletes returning to play. In several studies on collegiate and professional athletes, the prevalence of acute myocarditis varied from 1.4–15%,^{85–94} with larger series reporting a prevalence of 2–3%.^{87,94} Most athletes were asymptomatic and diagnosed with cardiac MRI alone. Almost all athletes had resolution of disease on repeat cardiac MRI. One series diagnosed myocarditis in 37 of 2810 US college athletes with cardiac MRI. The majority of athletes had resolution of myocardial oedema with resolution of T2 mapping abnormalities on cardiac MRI; although follow-up cardiac MRI for 27 (73.0%) athletes revealed that 11 (40.7%) had

persistent late gadolinium enhancement consistent with fibrosis.⁸⁷ In a follow-up study describing outcomes over a 1-year period of 3675 collegiate athletes who tested positive for SARS-CoV-2, 21 had definite or probable SARS-CoV-2 myocardial or myo-pericardial involvement by cardiac MRI.⁹⁵ All athletes were ultimately cleared for activity after a restricted period. After a 13.5-month follow-up period, 2 (0.05%) adverse cardiac events occurred, 1 involving sudden cardiac arrest related to a preexisting structural heart disease and the other involving new onset of atrial fibrillation less than 2 weeks after SARS-CoV-2 infection. This latter athlete underwent cardioversion without recurrence throughout the study period. To our knowledge, there are no studies regarding return to play in a paediatric population at the time of this review.

Consensus return to play guidelines have yet to be uniformly agreed upon. The American Academy of Pediatrics⁹⁶ advises that youths and adolescents with asymptomatic or mild disease complete at least 5 days of isolation, be fever free for 24 hours, and be evaluated by a medical provider prior to returning to play. Athletes should be without chest pain, shortness of breath out of proportion akin to an upper respiratory tract infection, palpitations or syncope. All athletes with any of these symptoms should be seen and examined in person by a trained medical provider. An ECG should be considered prior to returning to athletics. Athletes with at least moderate disease severity (≥ 4 days of fever; $>100.4^{\circ}\text{F}$ [$>38^{\circ}\text{C}$]; ≥ 1 week of myalgia, chills, or lethargy; or a non-ICU hospital stay and no evidence of MIS-C) should be cleared for return to sports after at least 10 days' rest, 7 days without symptoms, and after being seen by their physician with a complete history (emphasising symptoms of myocarditis), physical exam and ECG. If all results are reassuring, athletes are to return to sports gradually.⁹⁷ The optimal duration of this process is unknown and likely dependent on disease severity and fitness level.⁹⁸ If the screening is non-reassuring or if symptoms develop, further cardiovascular evaluation is recommended.

Recommended cardiac evaluation starts with examination, troponin testing, ECG and echocardiogram. Troponins, used to screen for COVID-19 induced cardiac injury, must be performed 24–48 hours after exercise and repeated if abnormal, as exercise can lead to troponin elevation. If the initial cardiac testing is abnormal, further testing with cardiac MRI, ambulatory ECG monitoring, and/or exercise testing should be considered. If troponins are elevated and cardiac MRI is normal but clinical presentation is consistent with cardiac disease, exercise should be restricted for 3 months. If clinical presentation is not

consistent with cardiac disease, the athlete may be considered for more rapid return to play with close monitoring. Athletes should not return to play if ventricular function is depressed, markers of myocardial injury or heart failure remain abnormal, and/or if there are arrhythmias on Holter monitor or exercise testing.⁹⁸

CONCLUSION

SARS-CoV-2 led to a global pandemic with significant mortality and morbidity. Cardiovascular disease is a striking feature of the clinical presentation in both adults and children. The virus—either through direct viral invasion or as a consequence of a dysregulated immune response—leads to myocardial injury with consequential arrhythmia, ventricular dysfunction, and/or shock. These consequences are seen during acute COVID-19 infection, post-infection and following mRNA vaccination. Patients with post-infectious hyperinflammatory syndromes, such as MIS-C, often have significant myocardial involvement; immunomodulatory therapies, such as IVIG and glucocorticoids are indicated.⁹⁹ Most infants, children and adolescents afflicted by COVID-19 cardiac disease fully recover with no lasting cardiac dysfunction; however, long-term studies are needed. As the virus evolves over time, the impact on the paediatric population and clinical disease will undoubtedly change.¹⁰⁰ Recommendations regarding vaccination and return to play will undergo several revisions to report dynamic changes in evidence-based best practices based on new developing data.

Children seeking medical care with or following acute COVID-19 should be screened for cardiac dysfunction. Patients with symptoms of decreased energy, fatigue, shortness of breath, swelling, chest pain, palpitations and/or decreased appetite; and/or with exam findings of abnormal heart rhythm or rate, abnormal precordial exam or heart tones including a rub or gallop, poor perfusion, rales, tachypnoea, hepatomegaly, jugular distention, and/or end organ dysfunction should undergo further cardiovascular evaluation. Consider screening for arrhythmia with an ECG and continuous cardiac monitoring in those patients admitted with severe acute COVID-19 or MIS-C. In patients with concerning history or physical exam, troponin and BNP or NT-pro-BNP are helpful screening labs for myocardial involvement and dysfunction. Both tests correlate with disease severity, although somewhat inconsistently;^{38,52,101} further investigation is needed to use these tests for prognostication. Echocardiography with strain and/or cardiac MRI should be considered to evaluate diastolic and systolic dysfunction, coronary anatomy, pericardium and

myocardium in paediatric patients with signs and symptoms of cardiac involvement. Consider exercise testing prior to returning to athletics for patients with arrhythmias or persistent abnormalities on cardiac imaging. In those with anatomic abnormalities, serial imaging should be performed until normalisation occurs. Patients with persistent dysfunction will benefit from close follow-up by a paediatric cardiologist.

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