Coronavirus disease 2019 and the young heart: prevention, treatment, and return to play

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Purpose of review
COVID-19-related guidance has changed dramatically since the onset of the pandemic. Awareness of data regarding prevention of disease, the cardiac manifestations and treatment of acute COVID-19 and multisystem inflammatory syndrome in children, and return to physical activity following an infection allows for appropriate adjustment of current care models and guides future study.

Recent findings
Severe acute respiratory syndrome coronavirus 2 transmission can be reduced using various mitigation strategies, though their effectiveness differs based on viral prevalence. The risk of severe disease during acute COVID-19 infection is low in children and adolescents, though specific risk factors have been identified. COVID-19 vaccination significantly decreases the risk of severe disease and poor outcomes. Regular physical activity positively affects well being and has been a focus of recent guidance regarding well tolerated return to activities following an infection.

Summary
The use of strategies to reduce viral transmission will depend on individuals' and communities' risk tolerance and on current viral prevalence. COVID-19 vaccination should be encouraged, particularly in patients with identified risk factors. Allowing children and adolescents to safely participate in physical and other activities should continue to be a focus of our clinical and research efforts given their myriad benefits in this population.

Keywords
coronavirus disease 2019, multisystem inflammatory syndrome in children, myocarditis, vaccination

INTRODUCTION

As of June 2022, there have been over 13 million pediatric cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the United States alone [1]. While children and adolescents typically have mild disease during acute infection, there remains a small risk for severe illness and even death during an acute illness and in the weeks to months that follow. Cardiac manifestations of coronavirus disease 2019 (COVID-19) may include cardiogenic shock, myocarditis, and arrhythmias. In this review, we discuss measures that have been taken to prevent SARS-CoV-2 infection in the pediatric population, cardiac manifestations, and the treatment of both acute COVID-19 disease and multisystem inflammatory syndrome in children (MIS-C), and an approach to well tolerated return to athletic activities following a COVID-19 diagnosis. Guidance changes dramatically as new information is learned and as risk profiles and individual and community needs change. The availability of COVID-19 vaccines, dynamic viral prevalence within communities, approval of therapeutics, and recognition that some degree of viral spread will likely continue in the years to come continue to adjust the landscape.

PREVENTION OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION IN THE PEDIATRIC PATIENT

At the start of the COVID-19 pandemic, nearly all forms of social engagement came to a halt to minimize the transmission of SARS-CoV-2. Despite the costs of physical distancing, this tactic was employed to reduce viral spread as the world learned about the virus's alarming transmission and risks.

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KEY POINTS

- Strategies used to mitigate the risk of COVID-19 have changed dramatically over time as COVID-19 vaccines have become available, therapeutics have been approved, and risk tolerance has changed.
- Most pediatric patients have no or mild symptoms during acute COVID-19 disease, though there remains a small risk for severe disease in this population.
- COVID-19 vaccination significantly decreases the risk of severe acute COVID-19 disease and of severe MIS-C.
- 'Return to Play' algorithms are designed to identify a small group of patients at risk for cardiac disease after apparent recovery from acute disease and will likely change over time as risk profiles continue to change.
- Allowing pediatric patients to participate in physical and other activities should be prioritized given the benefits they have for physical, mental, and social health.

In-person schooling, physical activity, and sports participation have undeniable benefits in pediatric patients. The return to in-person schooling and adoption of mask mandates in various settings were controversial, with individual risk tolerance playing a substantial role in discussions. When evaluating the effectiveness of prevention measures, it should be noted that the effect size of any mitigation strategy is likely dependent on the current viral prevalence within the community.

Regular physical activity positively affects mental, emotional, and physical well being and is of particular importance during the COVID-19 pandemic because of widespread stress, anxiety, and isolation. Rates of obesity, physical deconditioning, anxiety, and depression have significantly increased in the pediatric population [2▪,3,4]. Allowing children and adolescents to return to their activities required a delicate balance between mitigating risk of COVID-19 transmission while encouraging the positive physical and psychosocial aspects of athletic participation.

Many guidelines have been put forth on national, state, and local levels regarding athletic participation during the COVID-19 pandemic. Masking, physical distancing, and use of well ventilated or outdoor venues have aided in mitigating SARS-CoV-2 transmission during athletic activities. The feasibility of incorporating these strategies varies widely depending on the activity and the location in which it takes place. Reassuringly, these measures have been shown to be successful when enacted properly. One survey of high-school athletic directors throughout the Unites States demonstrated that use of masks among athletes was associated with a decreased incidence of COVID-19, particularly for indoor sports [5]. Another survey of various soccer and volleyball programs throughout the United States using multiple COVID-19 risk reduction techniques, including masking, social distancing, and symptom monitoring demonstrated no significant difference in rates of infection between the teams and the general population [6]. Interestingly, while only a small percentage of cases in the study was attributable to sports participation, there was a higher rate of COVID-19 infection in volleyball compared with soccer programs. This finding supports the use of outdoor and well ventilated venues whenever possible as well as consideration of stricter guidelines for indoor sports. Although there is some concern among young athletes regarding the impact of masks on level of performance, most agree that masking is important in preventing the spread of COVID-19 and are willing to comply if this allows for participation [7].

In addition to these prevention measures, identification of exposure to SARS-CoV-2, expeditious testing for those with symptoms, and appropriate quarantine and isolation periods have proven essential. The American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC) continue to recommend that team officials and health departments be notified of any positive test so that contact tracing and appropriate isolation can be undertaken and the risk of transmission can be minimized [8].

Importantly, the approval of the COVID-19 vaccine for people 5 years of age and older has helped to minimize disease severity and reduce transmission. A particular benefit of vaccination in the pediatric population is a decreased incidence of and illness severity related to MIS-C, a severe inflammatory syndrome affecting multiple organ systems that is temporally associated with a prior COVID-19 infection. Recent data from the CDC evaluating a series of hospitalized patients with MIS-C demonstrated that vaccination was 91% successful in preventing MIS-C in patients 12–16 years of age. In this study, all 38 patients with MIS-C requiring life support were unvaccinated [9▪]. Despite these findings, rates of vaccination in this population remain suboptimal. As annual and preparticipation physical examinations are one of the most common reasons for athletes to see their primary care physicians, these visits provide opportunities to educate families and provide COVID-19 vaccination [10]. The AAP has revised sports preparticipation history and physical examination forms to include questions regarding

COVID-19 history and COVID-19 vaccination status and continues to encourage all eligible children and adolescents to receive the COVID-19 vaccine [8].

CARDIAC MANIFESTATIONS AND TREATMENT OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION IN THE PEDIATRIC POPULATION

Fortunately, many children with acute COVID-19 infection have mild or even asymptomatic disease and are less likely than adults to become severely ill [11]. However, severe illness and death because of acute COVID-19 are still known to occur in this population. In addition, some children and adolescents may develop MIS-C. As of 5 June 2022, patients younger than 18 years of age accounted for 1523 of the total COVID-19-related United States deaths [1].

Children with underlying medical conditions appear to have higher risk for severe illness, although there are limited data regarding which medical conditions are associated with increased risk. Several studies have aimed to identify which pediatric patients are at the highest risk for significant illness. A large retrospective case series described the demographics and clinical characteristics of SARS-CoV-2-associated deaths in patients less than 21 years of age. Predominantly these patients were male individuals (63%), black (28%), and Hispanic (46%) persons and had at least one comorbid condition, most commonly obesity (42%) and asthma (29%) [12▪]. Eighteen percentage of those had cardiovascular disease, including congenital heart disease. Williams, *et al.* aimed to identify underlying comorbidities associated with severe disease and death in pediatric patients. They identified 108 patients (1.9%) with severe illness requiring mechanical ventilation out of a total of 5685 participants with documented SARS-CoV-2 infection [13▪]. Of those with severe illness, 75% had documented comorbidities. The most common of the comorbidities was underlying cardiac disease (23%) [13▪]. In a systemic review examining the link between COVID-19 and cardiac involvement in pediatric patients, previous cardiac surgery for newborns and children was related to risk of more severe illness, suggesting that congenital heart disease is a predisposing factor [14]. Further study is needed to determine the associated risk for patients with congenital heart disease.

Most often, treatment for acute COVID-19 consists of supportive care. For those with significant respiratory illness, this may include noninvasive respiratory support or intubation for mechanical ventilation. Significant cardiovascular manifestations of acute COVID-19 infection are less common, although there have been reports of cardiogenic shock, acute myocarditis, and arrhythmias including atrial and ventricular tachycardia [15,16]. Patients with severe disease may require intensive medical and supportive therapies including extracorporeal membrane oxygenation (ECMO) [16].

Immunomodulation and antiviral therapy may be indicated for those with or at risk for severe illness with SARS-CoV-2 infection. Remdesivir is the only US Food and Drug Administration (FDA)-approved medication for the treatment of hospitalized children (28 days or older and at least 3 kg). It is also approved for those who are not hospitalized but who have mild-to-moderate disease and are at high risk for disease progression. In a randomized controlled trial of nonhospitalized patients at least 12 years of age with at least one comorbid condition putting the patient at higher risk for progression, early administration of remdesivir resulted in an 87% lower risk of hospitalization or death compared with placebo [17▪▪]. The FDA has issued Emergent Use Authorizations for SARS-CoV-2 monoclonal antibodies and oral antivirals for use in high-risk persons. The emergence of SARS-CoV-2 variants continues to alter the options of directed therapies; as such, the effectiveness of monoclonal antibodies will vary depending on the predominant variant [18]. At this time, FDA emergency use criteria allows use of monoclonal antibodies in children at least 12 years of age and at least 40 kg who meet high-risk criteria. It is important to note that there is a dearth of data regarding the efficacy and safety of these monoclonal directed therapies while there is also a lack of clearly identifiable risk factors. As a result, an individualized assessment of the risks and benefits of direct therapies is recommended.

MIS-C typically occurs 2–6 weeks after acute SARS-CoV-2 infection. Compared with acute COVID-19 infection, MIS-C is less commonly seen in those with underlying medical conditions but does seem to affect Hispanic or black persons more commonly [19]. Cardiac involvement in MIS-C is common and includes ventricular dysfunction, coronary artery dilation, elevation in cardiac biomarkers, and pericardial effusion. Treatment is aimed at immunomodulation and has included intravenous immunoglobulin, steroids, and other agents, such as anakinra. Those critically ill with distributive and/or cardiogenic shock may require inotropic and pressor support, and rarely ECMO support. A multidisciplinary approach including specialists in rheumatology, cardiology, and infectious disease is beneficial. Outcomes are fortunately very good, with most patients demonstrating recovery of inflammation and cardiac function within weeks of the onset of acute illness. However, long-

term prognosis is still unknown and cardiology follow-up is recommended. The National Heart, Lung and Blood Institute is currently funding prospective 5-year follow-up data collection for patients diagnosed with MIS-C; these data will hopefully shed light on mid-term and long-term outcomes.

RETURN TO ATHLETIC ACTIVITIES FOLLOWING SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION IN THE PEDIATRIC PATIENT

The return to organized activities in late 2020 and early 2021 brought a need for structured guidance regarding disease prevention and safe return to play following COVID-19 infection. The potential for infection to cause myocarditis and MIS-C led to concern in children and adolescents, their families, and their providers. Due to the quickly recognized risk of myocarditis during acute infection and the known risk of exercise-related life-threatening arrhythmias in patients with myocarditis, several studies addressing myocarditis following COVID-19 in athletes garnered much attention in the latter half of 2020. Rajpal *et al.* [20] published a report of myocarditis in 4 (15%) of 26 athletes from The Ohio State University with PCR-confirmed SARS-CoV-2 infection after a work-up with ECG, troponin measurement, transthoracic echocardiogram, and cardiac MRI. All athletes in this study had had no or mild symptoms during their acute infections.

Since that time, multiple studies have suggested a lower risk of myocarditis in well athletes of college age and older following apparent recovery from acute COVID-19 infection [21,22,23▪,24]. Among 1597 collegiate athletes in the Big Ten COVID-19 Cardiac Registry, the prevalence of clinical myocarditis with a symptom-based screening strategy was 0.3%, whereas the use of MRI increased the prevalence of all (both clinical and subclinical) myocarditis to 2.3% [24]. Other studies have shown similar results, reporting a 0.7–3.3% prevalence of myocarditis or pericarditis following COVID-19 infection, with results varying based on the evaluation strategy [21,22,23▪,25▪]. Although these numbers are far lower than those initially reported, they suggest a measurable risk of COVID-19-related cardiac disease following apparent recovery from acute COVID-19. There are few reports evaluating the prevalence of COVID-19-related cardiac disease in younger patients, though some suggest a similar prevalence to that seen in older patients [26].

Numerous organizations have proposed COVID-19 'Return to Play' algorithms in an effort to identify patients at increased risk. As there was minimal evidence on which to base initial pediatric algorithms, individual institutions took local resources and opinions into account and intermittently updated their guidelines based on published data. Pediatric algorithms have typically taken both acute disease severity and the presence of potentially cardiopulmonary symptoms into account. Most algorithms recommend that patients with potentially cardiac symptoms such as chest pain, palpitations, shortness of breath out of proportion to an upper respiratory infection, or syncope undergo a cardiac evaluation prior to return to sports, as patients with these symptoms have been found to have an increased risk of COVID-19-related inflammatory heart disease [23▪]. It should be noted that deconditioned patients often experience shortness of breath and palpitations; an individualized and discerning evaluation of symptoms can help to identify the most appropriate management strategy. Patients without potentially cardiac symptoms are assessed based on the severity of acute disease, with specific recommendations varying among algorithms. Evaluation may include a pediatric cardiology referral, ECG, echocardiogram, and/or troponin measurement. Cardiac MRI is typically performed when a concern arises during the initial evaluation, as its yield is optimal in patients with a higher pretest probability of disease. The American Academy of Pediatrics' widely used 'Return to Play' and other similar algorithms will undoubtedly be revised over time as more data are available. The impact of vaccination status on a patient's risk for cardiac disease following apparent recovery from acute disease, for example, has not yet been factored into these algorithms on a large scale.

In addition to providing guidance about *when* an athlete may return to play, the AAP and other institutions have suggested *how* an athlete can return to play in a safe and successful way. Many variations of a gradual 'Return to Play' protocol have been used. In general, a gradual increase in the intensity and duration of exercise over a minimum of 3 days is suggested. This allows an athlete to identify the onset of potentially important symptoms during a lower risk activity and, perhaps more importantly, to allow the body a conditioning period to ease symptoms of the inevitable deconditioning that has occurred during the athlete's recent infection.

For patients who have been diagnosed with COVID-19-related myocarditis and/or MIS-C, guidance regarding return to sports and other activities is individualized and is likely to be similar to that for patients with other causes of myocarditis.

CONCLUSION

The COVID-19 pandemic has swept the globe and has affected many aspects of our lives. Preventive

measures have evolved over time as knowledge has been gained regarding their effectiveness and as more emphasis has been placed on finding well tolerated ways to allow young persons to participate in the activities that are so vital to physical and mental health. The availability of the COVID-19 vaccination for most pediatric patients has further altered the approach to disease prevention, though vaccination rates in this population remain suboptimal. Several treatment options are now available for hospitalized and at-risk patients with acute COVID-19 disease or MIS-C. The physical, emotional, mental, and social health benefits of physical and other activities will continue to play a role in guidance for the pediatric population as we adjust to the rapidly changing COVID-19 landscape.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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