



Role of a Pediatric Cardiologist in the COVID-19 Pandemic

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Abstract

Coronavirus disease 2019 (COVID-19) has affected patients across all age groups, with a wide range of illness severity from asymptomatic carriers to severe multi-organ dysfunction and death. Although early reports have shown that younger age groups experience less severe disease than older adults, our understanding of this phenomenon is in continuous evolution. Recently, a severe multisystem inflammatory syndrome in children (MIS-C), with active or recent COVID-19 infection, has been increasingly reported. Children with MIS-C may demonstrate signs and symptoms of Kawasaki disease, but also have some distinct differences. These children have more frequent and severe gastrointestinal symptoms and are more likely to present with a shock-like presentation. Moreover, they often present with cardiovascular involvement including myocardial dysfunction, valvulitis, and coronary artery dilation or aneurysms. Here, we present a review of the literature and summary of our current understanding of cardiovascular involvement in children with COVID-19 or MIS-C and identifying the role of a pediatric cardiologist in caring for these patients.

Keywords COVID-19 · Pediatric · Cardiovascular · MIS-C

Abbreviations

AAP	American Academy of Pediatrics	CMS	Centers for Medicare and Medicaid Services
ACC	American College of Cardiology	COVID-19	Coronavirus disease 2019
AHA	American Heart Association	CRP	C-reactive protein
ASE	American Society of Echocardiography	CTA	Computed tomographic angiography
BNP	Brain natriuretic peptide	ECG	Electrocardiogram
CDC	Center for Disease Control and Prevention	ECMO	Extracorporeal membrane oxygenation
CHIP	Child's Health Insurance Program	EHB	Essential Health Benefit
CK	Creatine kinase	ESR	Erythrocyte sedimentation rate
CMR	Cardiac magnetic resonance	GI	Gastrointestinal

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ICU	Intensive care unit
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
MIS-C	Multisystem inflammatory syndrome in children
NT-pro-BNP	N terminal pro brain natriuretic peptide
PIMS	Pediatric inflammatory multisystem syndrome
PMIS	Pediatric multisystem inflammatory syndrome
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SNAP	Supplemental Nutrition Assistance Program
UK	United Kingdom
VT	Ventricular tachycardia
WHO	World Health Organization
WIC	Women, Infants and Children

Introduction

A global pandemic was declared by the World Health Organization (WHO) on March 11, 2020 when the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spiraled into a global health crisis [1]. COVID-19 has created unprecedented challenges from public health, economic, medical, and research standpoints. It has been reported across all age groups and leading to a wide spectrum of illness severity from asymptomatic carriers to severe multi-organ dysfunction and death. Early observational studies have reported less severe presentation among children and young adults as compared to the older adults [2–7]. Rarely, children with active or recent infection with SARS-CoV-2 can also present with a severe inflammatory syndrome and features similar to those encountered in Kawasaki disease [8–11]. In Bergamo province of Italy, a 30-fold increase in the incidence of Kawasaki-like disease in comparison to the last five years has been described [8]. As of May 2020, the New York State Department of Health has also identified over 200 children with similar presentations [12]. This novel presentation has been termed as multisystem inflammatory syndrome in children (MIS-C) [12, 13], or pediatric multisystem inflammatory syndrome (PMIS) [14] or pediatric inflammatory multisystem syndrome (PIMS) [15]—these terms are used interchangeably in this article.

With an evolving understanding of this disease and rapidly expanding literature, keeping up with the clinically relevant information is important to our patients and us as clinicians. Here we present a summary of our current

understanding of the role of a pediatric cardiologist in caring for children and adolescents with COVID-19 and MIS-C.

Case Definitions

COVID-19

The WHO has proposed case definitions for COVID-19 that are regularly updated based on new evidence (Table 1) [1, 16]. Generally cases are classified as suspect, probable or confirmed based on the presence of acute respiratory symptoms, exposure and travel history in addition to confirmatory COVID-19 testing.

MIS-C

For children with MIS-C, two current definitions have been proposed, that may be subject to change as more evidence becomes available (Table 1). The initial case definition for MIS-C was proposed by the Royal College of Paediatrics and Child Health in UK and subsequently accepted by the WHO, Center for Disease Control and Prevention (CDC) and European Center for Disease Prevention and Control [14, 15, 17]. This definition was broad and included children under the age of 21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with current or recent history (within 4 weeks) of SARS-CoV-2 infection or exposure. This initial classification was able to identify all the pediatric patients within a critical spectrum of the disease that often required intensive care. Nevertheless, a less severe expression of the disease was also being seen and soon after, the WHO provided a more inclusive definition recognizing additional patients who did not require escalation of care. The age cut off was decreased to 19 years, fever duration of 3 days was introduced in the criteria and a combination of clinical, laboratory and microbiological criteria were also introduced in order to embrace all the patients under the same diagnosis (Table 1) [18].

Differences Between Children and Adults

There are numerous differences between children and adults with regards to disease prevalence, severity and complications of COVID-19 (Table 2). The percentage of children affected by COVID-19 is much lower than adults and they tend to have milder symptoms and significantly lower morbidity and mortality [2–7, 14, 19, 20]. Some of the frequently reported cardiac manifestations of COVID-19 in adults include; myocardial injury, myocardial dysfunction, myocardial infarction, Takotsubo cardiomyopathy, cardiogenic shock, pericardial

Table 1 Case definitions of COVID-19 and MIS-C

WHO case definitions of COVID-19	
Suspect case	Acute respiratory illness AND a history of travel or residence in a location with community transmission or contact with a confirmed or probable case of COVID-19 in the last 14 days prior to symptoms OR exposure to confirmed or probable COVID-19 case in 14 days prior to symptoms onset OR Severe acute respiratory illness requiring hospitalization in the absence of alternative diagnosis
Probable case	A suspect case with inconclusive COVID-19 testing or if testing could not be performed for any reason
Confirmed case	Patient with laboratory confirmation of COVID-19 irrespective of clinical signs or symptoms
<i>Illness severity</i>	<i>Mild/moderate</i> No new or increased supplemental oxygen requirement <i>Severe</i> New or increased supplemental oxygen requirement without needing new or increased non-invasive/invasive mechanical ventilation <i>Critical</i> New or increased non-invasive/invasive mechanical ventilation requirement OR presence of sepsis or multi-organ failure or rapidly worsening clinical trajectory
Case definitions of MIS-C	
CDC definition	Age <21 years presenting with fever (38 °C for at least 24 h), laboratory evidence of inflammation and evidence of clinically severe illness requiring hospitalization with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) with no alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection (RT-PCR, serology or antigen test) or COVID-19 exposure within 4 weeks prior to symptoms onset
WHO definition	Age 0–19 years with fever > 3 days AND at least two of the following: (i) Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation (ii) Hypotension or shock (iii) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (echo findings, elevated troponin/BNP) (iv) Evidence of coagulopathy (prolonged PT or PTT, elevated D-Dimer) (v) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation (ESR, CRP, Procalcitonin) with no other obvious microbial cause of inflammation AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

COVID-19 coronavirus disease 2019, *MIS-C/PMIS* multisystem inflammatory syndrome in children/pediatric multisystem inflammatory syndrome, *RT-PCR* reverse transcription polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus

effusion, arrhythmias, and conduction abnormalities, but these manifestations are quite rare in pediatric patients [21–27]. The cardiac findings encountered to date in the pediatric population include myocarditis, myocardial dysfunction and coronary artery involvement in MIS-C [8, 10, 12, 28–31]. In adults patients, comorbidities such as hypertension, diabetes, and obesity may predispose them to more severe manifestations of the disease [4, 32, 33]. In children, those that have comorbidities including medical complexity (dependent on technological support in association with developmental delay and/or genetic anomalies), obesity and those less than a year of age, seem to be at a risk for more severe disease [3, 34].

Clinical History and Physical Examination

COVID-19

A thorough history and physical examination is crucial in the diagnosis and assessment of a suspected COVID-19 patient. A detailed history of comorbid conditions, history of exposure to confirmed or probable cases of COVID-19 and travel history should be obtained. The most commonly reported symptoms in children are fever and cough [5, 34–40]. Some children present with gastrointestinal

Table 2 Difference between adults and children with COVID-19

	Adults	Children
Rates of infection	High	Low
<i>Evidence</i>	Chinese Center for Disease Control and Prevention reported only 2% of patients younger than 20 years of age among 44,672 cases [20] United States Center for Disease Control and Prevention (CDC) reported only 1.7% children less than 18 years of age among 149,082 reported cases [7]	
Severity of illness	High	Low
<i>Evidence</i>	<i>Chinese data:</i> 14% of adult patients classified as ‘severe’ and 5% as ‘critical’ disease [20] <i>Italian data:</i> 25% of adult patients classified as ‘severe’ and 5% as ‘critical’ [6]	<i>Chinese data:</i> 5% of pediatric patients classified as ‘severe’ and < 1% as ‘critical’ disease [36] <i>Italian data:</i> 2% of pediatric patients classified as ‘severe’ or ‘critical’ disease [5]
Complications and mortality	High	Low
<i>Evidence</i>	<i>United States data:</i> Among 2634 adults hospitalized in 12 hospitals in New York City, 14% required intensive care and 12% received mechanical ventilation with a case fatality rate of 21% [4] <i>Chinese data:</i> Case fatality 2.3% of overall COVID-19 affected population [20] <i>Italian data:</i> Case fatality of overall COVID-19 affected population 7% [6]	<i>United States data:</i> Among 46 North American Pediatric ICUs, only 48 children were admitted to intensive care with a case fatality rate of 4.2% [3] <i>Chinese data:</i> 1 death [36] <i>Italian data:</i> No deaths [5]
Potential risk factors leading to severe disease	Hypertension, diabetes, and obesity [4]	Infants < 1 years of age, medical complexity ^a , immune suppression, obesity [3, 5]

^aDefined as dependence on technological support (tracheostomy with or without ventilator dependence) in association with developmental delay and/or genetic anomalies

(GI) symptoms including nausea, vomiting, diarrhea or abdominal pain [34, 41–43]. Some cutaneous manifestations have also been reported in young patients such as ‘pseudo-chilblains’ described as areas of erythema with vesicles or pustules on hands and feet [44, 45]. Children with SARS-CoV-2 infection may also be asymptomatic carriers of the disease [7, 34, 35]. Other reported symptoms in adults include temporary loss of smell (anosmia) or taste (ageusia) sensation, headaches and thromboembolic phenomena [32, 33, 46–48].

MIS-C

In children with COVID-19, the latest concern is development of MIS-C, a Kawasaki-like syndrome with signs of heart failure or shock [8, 10, 12, 17, 49]. In multiple case series, as high as 50–80% of the children with MIS-C developed signs of systemic hypoperfusion or shock, which is contrary to Kawasaki disease where only up to 5% of the cases may require vasopressor support [8–10, 31, 50]. One of the clinical difference between MIS-C and Kawasaki syndrome is a higher incidence of GI symptoms in MIS-C related to SARS-CoV-2 than with classic Kawasaki disease. These GI symptoms include nausea, vomiting, diarrhea, and/or moderate to severe abdominal pain sometimes mimicking acute appendicitis or enteritis [10, 31, 50, 51]. In children with MIS-C, there is multisystem organ involvement including cardiac, renal, hematological,

or neurological manifestations [8, 10, 12, 17, 31]. Severe respiratory symptoms are relatively rare in MIS-C [50]. Therefore, children presenting with persistent fever (≥ 38 °C or 100.4°F, ≥ 3 days), gastrointestinal complaints, rash, conjunctivitis, oral/mucosal changes, or cervical lymphadenopathy require assessment for MIS-C. Signs of heart failure such as edema, organomegaly, murmur, gallop or friction rub maybe present. It is essential to pay attention to the vital signs and hydration status of patients. However, MIS-C is still a rare phenomenon and other sources of infection that may cause fever or systemic inflammation should also be considered in differential diagnosis.

Microbiological Diagnosis

There are two categories of tests currently being utilized for the diagnosis of COVID-19 infection, *diagnostic tests* for identifying active infection and *serologic tests* to identify past infection. Diagnostic tests include direct detection of SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR) or detection of SARS-CoV-2 antigens by rapid antigen tests [52]. Detection of viral RNA by RT-PCR, from nasopharyngeal swab or other upper respiratory tract specimens, is the most commonly used and reliable test [53]. Although RT-PCR is highly specific for the virus, negative tests should be interpreted with caution as the specificity of the test depends on the type of assay, site

and quality of specimen obtained in addition to the timeline of illness at the time of testing [53, 54]. Rapid antigen tests are also available for the diagnosis of active infection but are less commonly used. They are less sensitive than RT-PCR but are highly specific for the virus [55]. Serologic tests detect antibodies (IgM and IgG) to SARS-CoV-2 and are generally suggestive of a past infection. Serologic tests demand careful interpretation based on timeline of infection [53].

Laboratory Abnormalities

Common laboratory findings in hospitalized adult patients with COVID-19 include lymphopenia, neutrophilia, and elevations of serum amino-transaminases, lactate dehydrogenase (LDH), creatine kinase (CK) and other inflammatory markers such as C-reactive protein (CRP), procalcitonin, ferritin and erythrocyte sedimentation rate (ESR) [32, 38, 39]. Elevation of troponin and brain natriuretic peptide (BNP) or N terminal pro BNP (NT-pro-BNP) is associated with admission to the ICU, intubation, and death in adult patients [21, 32, 38, 56–60]. These laboratory abnormalities have also been reported in children, but data are limited due to a relative lack of studies focused on the pediatric population [61, 62]. Children presenting with MIS-C consistently demonstrate these laboratory abnormalities including elevated Troponin and BNP levels [8, 10, 12, 15, 17, 50]. Additionally thrombocytopenia, elevated D-dimer, elevated fibrinogen and hypoalbuminemia may be seen [8–10, 15, 50].

Pathophysiology of Cardiovascular Manifestations

The etiopathogenesis of cardiovascular manifestations in COVID-19 are unclear. Several mechanisms have been proposed including direct myocyte injury from viral infection, myocardial inflammation, myocardial ischemia/infarction, hypoxia induced apoptosis, microvascular disease, and cytokine storm [63]. A direct correlation between CRP and troponin levels has been shown suggesting an additional inflammatory role in the pathogenesis of the clinical manifestations [60]. Downregulation of the myocardial protective enzyme angiotensin converting enzyme 2 (ACE-2) by SARS-CoV-2 has also been proposed as a potential mechanism of injury to the myocardium [64]. The mechanism of coronary artery dilation may be extrapolated from Kawasaki disease and inflammatory vasculopathy [65]. Myocardial dysfunction, coronary artery involvement, and factors like hypoxia, electrolyte abnormalities, QT prolonging medications may predispose these patients to various arrhythmias [66, 67].

Approach to Evaluation and Indications for Pediatric Cardiology Referral

A general approach towards the evaluation of COVID-19 and MIS-C, as guided by the most recent recommendation by the CDC and American Academy of Pediatrics (AAP), is shown in Fig. 1. [14, 17, 68, 69] Pediatric cardiology may be consulted for patients with COVID-19 with a concern for cardiac involvement or those with MIS-C (Fig. 3). Presence of chest pain, palpitations, persistent tachycardia, tachypnea, or new murmurs should prompt further evaluation by laboratory testing, electrocardiogram (ECG) or echocardiogram. Laboratory evaluation in patients with significant cardiac symptoms should also include measurement of biomarkers such as troponin or BNP/NT-pro-BNP. An ECG may be considered in patients with concerning cardiac symptoms, elevated cardiac biomarkers, or prior to initiation of any therapy that could prolong the QT interval. Those with elevated troponin and BNP/NT-pro-BNP may also benefit from an echocardiogram. Patients with cardiogenic and/or distributive shock in the intensive care should prompt a pediatric cardiology consultation.

Electrocardiographic Abnormalities and Arrhythmia

Patients affected with COVID-19 or MIS-C may be predisposed to various arrhythmias or electrocardiographic (ECG) abnormalities, not only from the disease itself but also from the arrhythmogenic potential of pharmacotherapies. In adults, a higher prevalence of both atrial [38] and ventricular arrhythmias [59] were noted among hospitalized patients with COVID-19 which has been linked to an increased risk of in-hospital death [59].

Possible ECG findings in children with COVID-19 or MIS-C are listed in Table 3 and shown in Fig. 2. In patients with myocardial dysfunction, diffuse ST segment changes, T wave inversions in lateral leads, low-voltage QRS, atrioventricular conduction block and sinus node dysfunction has been reported [26, 70–74]. Premature ventricular contractions [30], monomorphic [74] or polymorphic ventricular tachycardia (VT) [50] have also been reported. Patients with MIS-C may present with ECG abnormalities similar to those expressed in Kawasaki disease (Table 3) [9, 10]. QT prolongation can be seen in critically ill patients with systemic inflammation, fever, electrolyte abnormalities or hypoxia. In addition pharmacotherapies for COVID-19 such as hydroxychloroquine and azithromycin may cause fatal arrhythmias due to QT prolongation [75–77]. It is important to obtain a baseline

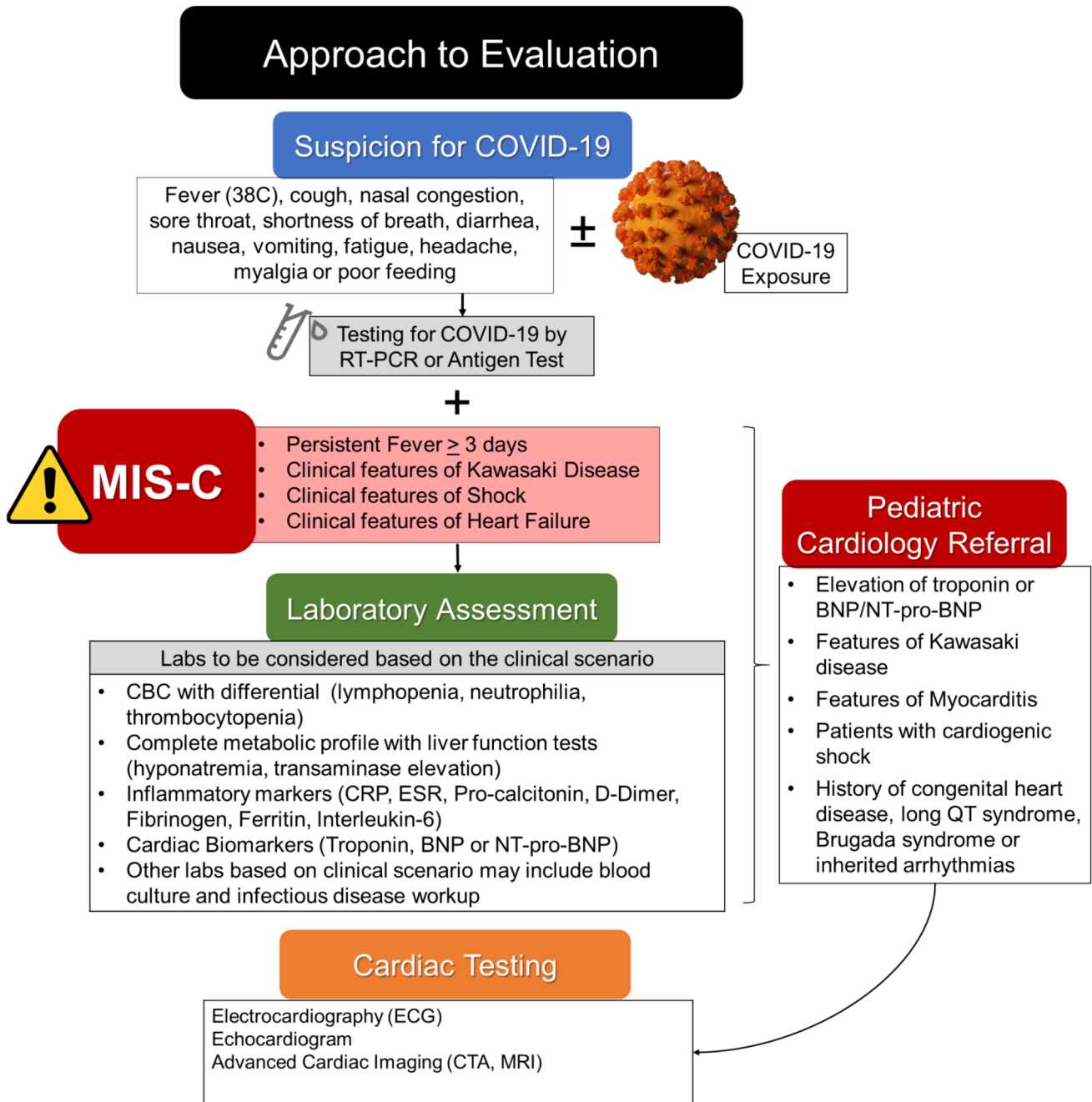


Fig. 1 Approach in children with COVID-19 and MIS-C with red flags for pediatric cardiology referral

ECG in patients with COVID-19 to measure a baseline QT interval, especially in those with congenital long QT syndrome or other genetic arrhythmias [75, 78–80]. Fever in patients with COVID-19 may unmask the classic Brugada pattern on ECG [67, 75, 76, 81, 82].

Table 3 Potential electrocardiographic and echocardiographic findings in MIS-C

<i>Electrocardiographic abnormalities and arrhythmias</i>	
Abnormalities related to myocardial dysfunction or myocarditis	Diffuse ST segment elevation or depression T wave abnormality (inversion in lateral leads) Low QRS voltages Premature ventricular contractions Ventricular tachycardia
Abnormalities similar to Kawasaki disease	Non-specific ST and T wave changes Myocardial ischemia PR prolongation Ventricular arrhythmia
Sinus node dysfunction and heart block	Sinus node dysfunction (bradycardia) PR prolongation Atrioventricular block
Inherited arrhythmias and sudden death	Prolonged QT Unmasking of Brugada pattern in patients with underlying Brugada syndrome in setting of fever Sudden cardiac death due to fatal arrhythmias
<i>Echocardiographic abnormalities</i>	
Ventricles	Depressed function of either or both ventricles, may be severe and may exhibit global or regional dysfunction Abnormal myocardial strain Apical thrombus in setting of severely depressed function
Coronary arteries	Abnormal enhancement of coronary arterial walls Coronary arterial ectasia or dilation Aneurysm formation Thrombus formation in setting of severe coronary dilation
Valves	Valvulitis with valvar insufficiency, particularly the mitral valve
Pericardium	Pericardial effusion
Aortic root	Aortic root dilation

Cardiac Imaging

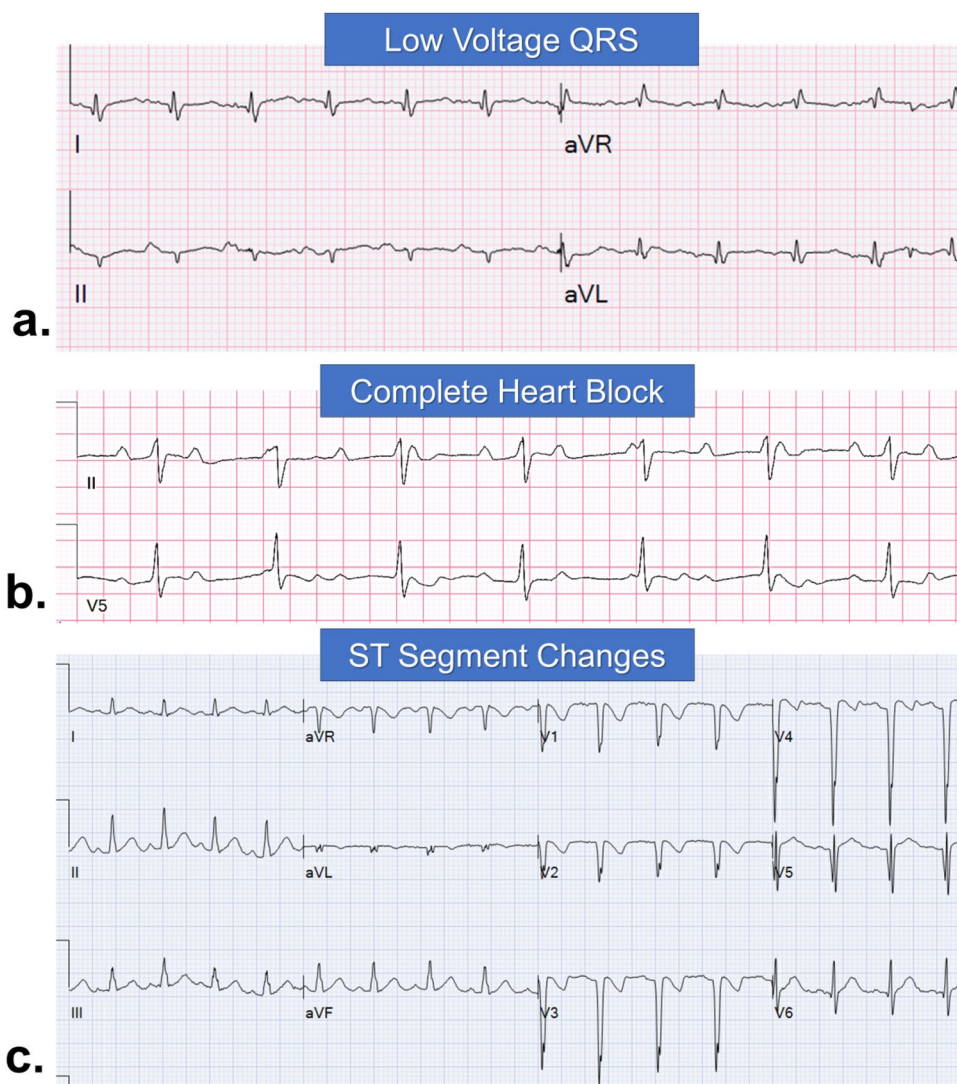
Echocardiographic Evaluation

During acute COVID-19 infection in hospitalized adult patients, echocardiographic features supportive of myopericarditis, stress-induced cardiomyopathy, and/or myocardial ischemia, injury, or infarction have been described [83]. There may be global or segmental mild to severe myocardial dysfunction involving the left ventricle in isolation or both ventricles [22, 23]. Left ventricular apical ballooning and dysfunction consistent with Takotsubo cardiomyopathy [27, 84] as well as pericardial effusions have been reported [22, 23]. In the pediatric population, data are lacking regarding echocardiographic findings during the acute infection likely due to the decreased incidence of clinically severe illness compared with adults [3, 34, 37].

However, echocardiographic information is available for pediatric patients with MIS-C. The initial alert to the international community first identifying MIS-C described myocarditis, valvulitis, pericardial effusion, and coronary artery dilation as features of the disease [14]. Of the 8 children from the United Kingdom (UK) reported by Riphagen

et al., ventricular dysfunction was present in 6 patients. Only 1 child had severely dilated coronaries and 1 had pericoronary echogenicity [9]. Subsequently, Belhadjjer et al. reported data regarding 35 children with MIS-C with acute left ventricular dysfunction (68% with cardiogenic shock) [10]. One of these patients had localized akinesis of the apical segment consistent with Takotsubo cardiomyopathy. Fortunately, 71% recovered LV function fully by day 7 of illness with therapy [10]. Coronary artery dilation (Z score > 2) was present in only 17% and pericardial effusions were seen in 8%. Verdoni et al. reported 10 patients with features of typical or atypical Kawasaki Disease and COVID-19, with ventricular dysfunction (ejection fraction $< 55\%$) in 5, mitral insufficiency in 4 and coronary aneurysms (> 4 mm) in 2 patients [8]. Most recently, Whittaker et al. reported on 55 children from 8 hospitals in the UK who underwent echocardiography. Coronary dilation (Z score > 2) was noted in 8 (14%), including 2 with giant aneurysms (Z scores > 10). Of these eight, five had shock alone, one with fever and inflammation, and two with some mucocutaneous features of Kawasaki disease. Of the 29 children with shock, 62% had LV dysfunction on echo [50]. In a recent study from US constituting 186 children with MIS-C, Feldstein et al. reported

Fig. 2 Electrocardiographic abnormalities in children with COVID-19 and MIS-C. **a** Low-voltage QRS complex in a patient with myocarditis. **b** Complete heart block in a patient with myocarditis. **c** ST segment changes in anterior leads suggestive of anterior infarction in a patient with giant coronary artery aneurysms and thrombosis



coronary artery aneurysm (Z score > 2.5) in 9% (15/170) of the children who had echocardiogram [31].

For pediatric patients presenting with concern for MIS-C, hemodynamic shock and/or features of classic or atypical Kawasaki disease, a careful echocardiographic assessment (Table 3; Fig. 3) of left and right ventricular function, the pericardium, coronary arteries, and cardiac valves should be performed on admission to establish a baseline, as well as to guide initial vasoactive management for patients presenting with features of shock. It is important that the individual performing the echo have the skills to obtain all the necessary images in a time efficient manner to limit exposure. The American Society of Echocardiography (ASE) statement regarding echocardiography services during the COVID-19 pandemic can serve as a useful reference with regards to best practices [85]. The optimal interval between echocardiographic assessments remains to be determined. Primarily, a change in clinical status should guide the echocardiographic

evaluation in individual cases. For patients requiring ICU management, daily echocardiograms may be warranted given the potential for rapid changes. For those on acute care floors, repeat echocardiograms every 2–3 days may be helpful although should be guided by the clinical scenario. Serial echocardiographic assessment of the coronary arteries for evolving dilation or development of coronary aneurysms is important as well, as this will impact decisions regarding immunomodulatory therapies and anti-thrombotic regimens. Previously published guidelines for optimal coronary artery imaging in Kawasaki Disease can be utilized [65, 86]. For patients with severe ventricular dysfunction or severe coronary dilation, serial assessment for thrombus is important. All MIS-C or Kawasaki disease spectrum type patients should have a follow-up with a pediatric cardiologist with an echocardiogram. Timing of follow-up and imaging tests will depend upon the clinical course, as well as the type and severity of cardiac involvement. Long term outcomes

Echocardiographic Abnormalities

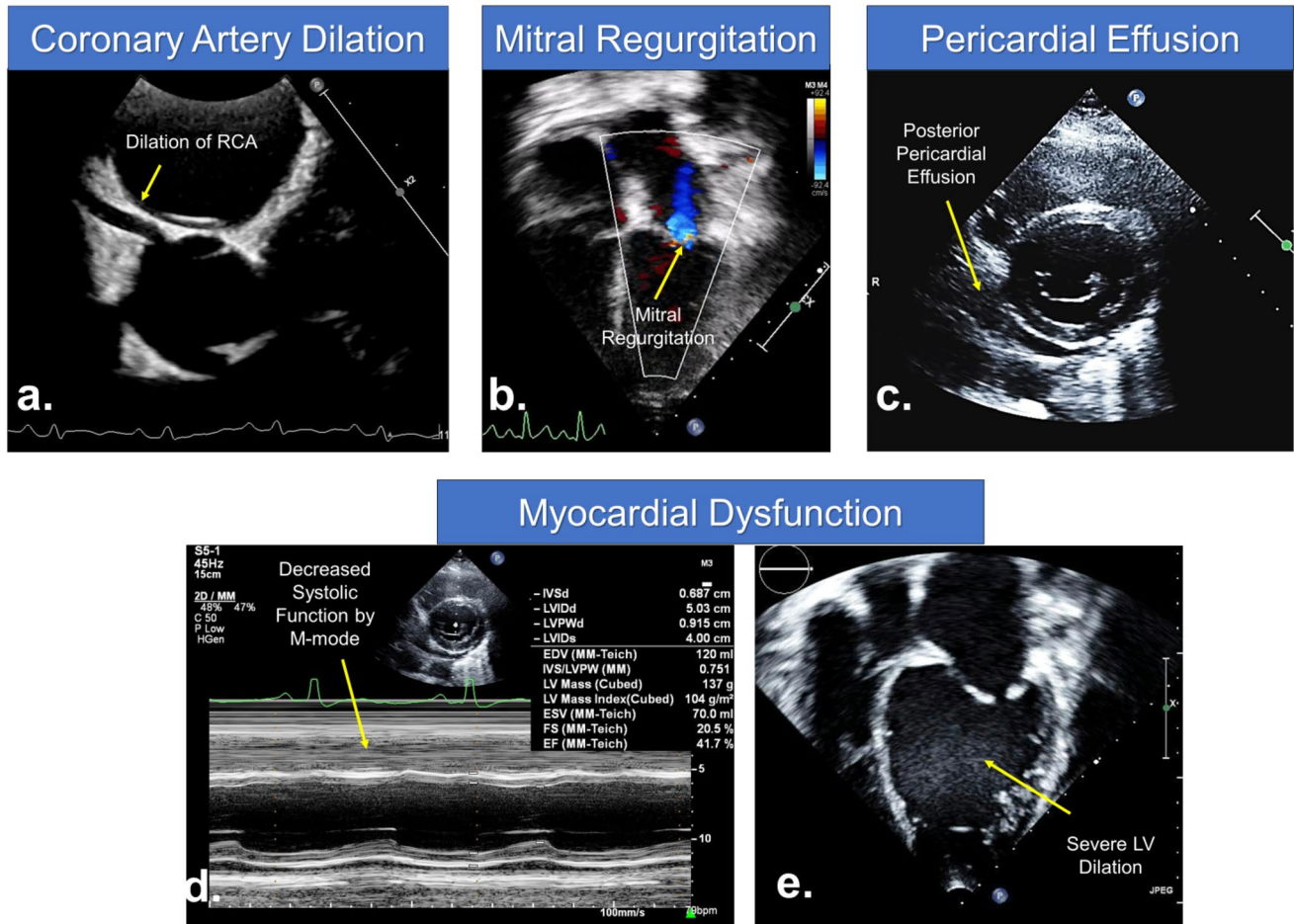


Fig. 3 Echocardiographic abnormalities in children with COVID-19 and MIS-C. **a** Parasternal short axis view at the level of aortic valve demonstrating diffuse dilation of right coronary artery (RCA) and coronary artery walls are echogenic. **b** Apical 4 chamber view demonstrating mitral valve regurgitation. **c** Parasternal short axis view at

the level of mitral valve showing tiny posterior pericardial effusion in a patient with myocarditis. **d** M-mode demonstrating decreased systolic function. **e** Apical 4 chamber view demonstrating severe left ventricular (LV) dilation due to myocardial dysfunction

of children with MIS-C are unknown. Patients with continued coronary artery abnormalities or depressed ventricular function should continue to follow with a pediatric cardiologist while these sequelae of MIS-C are present. Given the unknowns, even those with recovery of ventricular function or resolution of coronary dilation likely warrant continued follow-up over time.

Advanced Imaging

Advanced cardiac imaging with computed tomographic angiography (CTA) may be necessary for demonstration of coronary arteries in older children and adolescents if

poor acoustic windows limit echocardiographic assessment. Similar to Kawasaki disease, CTA also plays an important role in assessing distal vessels for evidence of dilation [65]. CTA is also critical in the evaluation of suspected coronary thrombus. Data regarding the use of cardiac magnetic resonance (CMR) imaging in the pediatric age group with COVID-19 are lacking although utilization of CMR imaging can be guided by previous evidence from viral myocarditis. Decisions should be made on case by case basis in consideration with the pediatric cardiologist. In the adult population, the utility of CMR has been described in a case report of myocarditis due to COVID-19, where it was used to confirm the diagnosis

Table 4 Considerations for management of children with COVID-19 or MIS-C and cardiovascular involvement*Considerations for management of typical COVID-19 with cardiovascular involvement*

General considerations	Supplemental oxygen, non-invasive or invasive mechanical ventilation may be needed for patients as appropriate Fluid replenishment and adequate electrolyte monitoring Empiric antibiotics as clinically appropriate Antiviral therapies are to be used in the settings of a clinical trial in discussion with an infectious disease team
Cardiac considerations	For myocardial dysfunction, arrhythmias or other manifestations, see management suggestions listed below

Considerations for management of MIS-C with cardiovascular involvement

General considerations	Level of care is determined by the severity of illness Given multisystem involvement, patients may benefit from care by a multidisciplinary team of specialists Sequential laboratory markers of inflammation, coagulation studies, liver function tests and cardiac biomarkers may be warranted in hospitalized patients Additional management, as appropriate, is as per the intensivist or hospitalist based on the clinical presentation
Myocardial dysfunction or myocarditis	Serial laboratory monitoring of cardiac biomarkers including troponin and BNP/NT-pro-BNP Serial echocardiographic assessment of myocardial function Continuous cardiac monitoring for arrhythmias Hemodynamic support utilizing inotropes and ECMO as indicated Care should be taken while sedating or intubating patients with severely depressed ventricular function Consideration for therapies such as IVIG, steroids or biological agents in the setting of a multidisciplinary team discussion regarding current evidence and best practices, risks and benefits
Arrhythmias	12 lead ECG may be obtained in all hospitalized children, those with elevated cardiac biomarkers or cardiac symptoms and before initiating any QT prolonging pharmacotherapies Aggressive fever reduction with acetaminophen is necessary for patients with Brugada syndrome Aggressive electrolyte correction is necessary for patients with inherited arrhythmias and channelopathies Modified ACLS and BLS guidelines should be utilized during cardiopulmonary resuscitation
Coronary artery and thrombotic complications	Antiplatelet therapy should be considered for patients with MIS-C Anticoagulation guided by Kawasaki guidelines can be utilized based on degree of coronary artery involvement Pediatric cardiology follow-up and serial echocardiographic assessment is critically important for patients with coronary artery dilation due to MIS-C

Considerations for children with underlying cardiovascular conditions

Chronic medications	Continue ACE inhibitors or ARBs in patients who are chronically receiving these therapies for hypertension, heart failure or other underlying diseases [66]
Anticoagulation	Certain exploratory antiviral therapies such as ropinavir/ritonavir, ribavirin, and adjunctive therapies such as sarilumab, tocilizumab interferon and methylprednisolone may interact with Warfarin. Therefore adequate INR monitoring should be performed with these therapies [66] Aspirin should be continued in children and adolescents on chronic therapy for their underlying cardiovascular condition
Immunosuppression	There is insufficient evidence regarding the potential role of reduction or changes in T-cell immunosuppressive therapy among infected patients after cardiac transplant patients with COVID-19. A detailed discussion with cardiac transplant team weighing risks and benefits of reduction in T-cell immunosuppression is warranted [16]

ACE angiotensin converting enzyme, ARBs angiotensin receptor blockers, ACLS advanced cardiac life support, BLS basic life support, BNP brain natriuretic peptide, INR international normalized ratio, MIS-C multisystem inflammatory syndrome in children

and to demonstrate the extent and severity of myocardial edema [30].

Management of Cardiovascular Complications in COVID-19

General Considerations

COVID-19 can lead to a wide spectrum of illness severity (Table 1) which guides the management [16]. Some general considerations for management of COVID-19 patients are stated in Table 4. The efficacy of various antiviral therapies in COVID-19 has yet to be established [16]. Therefore until more evidence is available; therapies such as remdesivir and hydroxychloroquine should be used in context of a clinical trial while weighing the risks and benefits of the therapy [16]. These decisions are individualized to every patient keeping in consideration the various risk factors including young age, immunocompromised status, underlying cardiac or pulmonary disease, obesity or diabetes [16].

Approach to Cardiovascular Complications

Myocardial Injury and Myocarditis

Although myocardial dysfunction is uncommon among children with typical COVID-19 infection; children presenting with MIS-C may have significant myocardial involvement [8–10, 50]. Evidence regarding optimal management of myocardial injury in patients with COVID-19 is limited. The management may be guided by the extent of myocardial injury based on laboratory (elevated Troponin or BNP/NT-pro-BNP) and imaging (echocardiography or CMR)

assessment. Serial monitoring of biomarkers is prudent during admission as detailed in the section on laboratory evaluation. *Hemodynamically stable* children with mild myocardial dysfunction should be medically managed and optimized with careful fluid resuscitation, diuretics and heart failure therapy as appropriate. Children with *hemodynamically significant* or severe myocardial dysfunction may require inotropic support, mechanical ventilation to reduce metabolic demand and mechanical circulatory support with extracorporeal membrane oxygenation (ECMO) in those with critical hemodynamic compromise [10]. Shock in patients with MIS-C is often vasoplegic rather than cardiogenic and the use of norepinehrine to treat is effective but treatment may be guided by the degree of ventricular dysfunction [9].

Children with MIS-C and myocardial dysfunction may warrant treatment with intravenous immunoglobulin (IVIG) and/or steroids although the evidence is currently limited (Table 5) [8–10, 50, 87]. In six case series constituting 314 patients with MIS-C or Kawasaki-like presentation, a majority of patients were initially treated with IVIG (77%, 241/314) with or without steroids (53%, 167/314) [8–10, 50, 87]. Other immunomodulatory agents like anakinara was used in 20 patients, 8 received infliximab and 1 received tocilizumab. Among studies with available data, almost half of the patients (50%, 64/128) received combined therapy with at least 2 immunomodulatory agents generally IVIG and steroids.

Arrhythmias

Although arrhythmias may be a rare manifestation of COVID-19, they are not uncommon in critically ill children with COVID-19 and MIS-C [9, 10, 75]. Critically ill patients with COVID-19 or MIS-C requiring intensive care or those

Table 5 Evidence on utilization of intravenous immune globulin and steroids in MIS-C

	Total No of Pts	IVIG	Steroids	Others	Combined therapy (≥ 2 agents)
Belhadjer et al. [10] (France and Switzerland)	35	71% (25)	34% (12)	Anakinara (3)	14% (5)
Riphagen et al. [9] (United Kingdom)	8	100% (8)	62% (5)	None	62% (5)
Verdoni et al. [8] (Italy)	10	100% (10)	80% (8)	None	80% (8)
Cheung et al. [87] (United States)	17	76% (13)	82% (14)	Tocilizumab (1)	65% (11)
Whittaker et al. [50] (England)	58	70% (41)	64% (37)	Anakinara (3) Infliximab (8)	60% (35)
Feldstein et al. [31] (United States)	186	77% (144)	49% (91)	Anakinara (14)	-
Combined studies	314	77% (241)	53% (167)		50% (64)

Values are reported as % (n)
IVIG intravenous immune globulin

with increased arrhythmia risk should be placed on continuous ECG monitoring [76]. Management should be tailored to the individual patient and arrhythmia. For instance in patients with Brugada syndrome, aggressive fever reduction with acetaminophen is prudent [77]. General considerations for management of arrhythmias are stated in Table 4. Additionally, the American Heart Association has released interim guidelines for basic and advanced life support in adults, children, and neonates with suspected or confirmed COVID-19 with attention to reducing provider exposure, prioritizing oxygenation and ventilation strategies, and considering the appropriateness of resuscitation [88].

Thrombotic Complications

Considering similarities between MIS-C and Kawasaki disease, these patients may also be at a higher risk of thrombotic complications. Among combined 278 patients from five recent studies who had echocardiograms, coronary dilation or aneurysm was reported in 12% (132/278) of patients [8, 10, 12]. Therefore, patients with MIS-C who fulfill criteria for Kawasaki disease, whether complete or incomplete, should be treated with appropriate anti-thrombotic therapy based on the degree of coronary artery involvement. Antiplatelet therapy should also be considered for all patients with MIS-C and evidence of coronary artery involvement [65]. Similarly patients with significant left ventricular dysfunction should also receive systemic anticoagulation as appropriate [89].

Pre-existing Cardiovascular Conditions

Children with congenital heart diseases or underlying cardiovascular conditions such as hypertension, heart failure or cardiac transplant pose certain unique challenges to their providers. It is critical to pay attention to their underlying disease process and chronic medications [16, 66]. Currently there is insufficient evidence to suggest any concern around safety of ACE inhibitors or Angiotensin receptor blockers (ARBs) in patients with COVID-19. Therefore multiple societies have endorsed and recommended to continue ACE inhibitors or ARBs therapy in patients who are chronically receiving these therapies for hypertension, heart failure or other underlying diseases [66]. Certain exploratory antiviral therapies like ropinavir/ritonavir, ribavirin, sarilumab, tocilizumab and adjunctive therapies like interferon or methylprednisolone may interact with Warfarin [66]. Therefore patients on chronic anticoagulation therapy should have adequate monitoring of INR while pursuing these therapies. Aspirin should be continued in children and adolescents on chronic therapy for their underlying cardiovascular condition. Currently there is insufficient evidence regarding role of reduction or changes in T-cell immunosuppressive

therapy among infected patients after cardiac transplant [16]. A detailed discussion with cardiac transplant team weighing risks and benefits of reduction in T-cell immunosuppression is warranted.

Outcome and Follow-up

In a recent study by Feldstein et al. constituting 186 children from US, 8 patients required ECMO and 4 deaths were reported [31]. Among 230 cases of suspected MIS-C associated with COVID-19 reported to European Centre for Disease Prevention and Control, at least two deaths have been reported [11]. Currently we do not have enough data to predict future complications in MIS-C associated with COVID-19. As we steer through this uncharted territory of COVID-19, we may have to extrapolate evidence from conditions with similar presentations such as viral myocarditis or Kawasaki disease. Recommendations for follow-up, long term anticoagulation return to school and sports participation should be individualized to every patient. Follow-up should be individualized based on the degree of myocardial dysfunction, arrhythmia burden, and cardiac biomarkers along with a potential role of advanced imaging with CMR, as per the guidelines by AHA and American College of Cardiology (ACC) [90, 91].

Cardiac Interventions

The COVID-19 pandemic has seriously affected surgical and interventional practices, both catheterization and electrophysiology, in pediatric and congenital cardiology [92, 93]. Majority of centers have canceled or rescheduled elective procedures during the first phase of the pandemic and utilized a multidisciplinary committee to determine the candidacy of patients for urgent or emergent procedures. The definition of elective, urgent or emergent procedures is dependent on institutional policy and various society guidelines are now available to guide decisions [93, 94]. Generally, procedures are considered urgent or emergent if there is a substantial risk of clinical decompensation, hospitalization, or death if procedures are not performed [93, 94]. It is necessary to maintain a focus on resource utilization, preservation of medical supplies and minimization of exposure to hospital staff and other patients while making these decisions [92]. Pre-procedural COVID-19 testing is being performed in many centers to ensure safety and adequate personal protective equipment (PPE) utilization by health care team. Recommendations related to PPE continue to change. There is a concern that there may be a backlog of purely elective cases, a so called “surge after the surge”, that

may continue on for months [95]. Each program should have a plan on how to deal with these cases [95].

Impact on the Economy and Insurance Policies

The negative effects of the COVID-19 pandemic on our national and global economy have been dramatic, affecting almost every industry. The majority of health insurance companies have followed the lead of the federal government and Centers for Medicare and Medicaid Services (CMS) to rapidly expand coverage to patients with COVID-19. All testing for COVID-19 has been designated an Essential Health Benefit (EHB), meaning it is to be covered by all Affordable Care Act—compliant plans. In March 2020, Congress passed the Families First Coronavirus Response Act [96] which requires the majority of private health plans to cover COVID-19 testing and all related urgent care center and emergency room visits, telehealth services, and in-person medical provider encounters, all with no cost sharing (co-payments, co-insurance and deductibles) and no prior authorization during the emergency period [96]. There continue to be discrepancies across states and insurance policies, so it is advised that the patient, physician and billing department stay abreast of this rapidly changing market and their implications. If patients are experiencing financial difficulties due to COVID-19, there are a number of government programs available, including but not limited to unemployment coverage: Supplemental Nutrition Assistance Program (SNAP), Women, Infants, and Children (WIC), Child's Health Insurance Program (CHIP) and Medicaid. For children, the CHIP offers free or low-cost medical and dental care to uninsured patients through 19 years of age, whose family income is above Medicaid's limit but below their state's CHIP limit. Many states have modified their CHIP enrollment criteria and dates to expand eligibility and eliminate or waive premiums. The CARES act and SBA loans have provided some financial support to medical practices and hospitals.

Future Directions

COVID-19 has had a profound impact on the practice of medicine and will continue to impact all elements of patient care. As more pediatric data become available, the approach to the evaluation and management of children with COVID-19, including those with suspicion for cardiac injury, will necessarily evolve. Pediatric cardiologists can have a meaningful impact in the care and outcomes of these patients.

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