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AHA SCIENTIFIC STATEMENT

SARS-CoV-2 Infection and Associated Cardiovascular Manifestations and Complications in Children and Young Adults: A Scientific Statement From the American Heart Association

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ABSTRACT: Coronavirus disease 2019 (COVID-19) resulted in a global pandemic and has overwhelmed health care systems worldwide. In this scientific statement, we describe the epidemiology, pathophysiology, clinical presentations, treatment, and outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and multisystem inflammatory syndrome in children and young adults with a focus on cardiovascular manifestations and complications. We review current knowledge about the health consequences of this illness in children and young adults with congenital and acquired heart disease, the public health burden and health disparities of this infection in these populations, and vaccine-associated myocarditis.

Key Words: AHA Scientific Statements ■ child ■ COVID-19 ■ multisystem inflammatory syndrome in children ■ SARS-CoV-2 ■ treatment outcome ■ young adult

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Coronavirus disease 2019 (COVID-19), which resulted in a global pandemic, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease presents acutely as cough, fever, and chills with ensuing shortness of breath and hypoxia. Cardiovascular complications from this infection in adults include myocardial injury, arrhythmias, acute coronary syndrome, and venous thromboembolism.[1–6] Preexisting cardiovascular diseases are associated with increased morbidity and mortality in adults with SARS-CoV-2 infection.[7] In contrast, most pediatric and adolescent patients infected with SARS-CoV-2 (Figure) are asymptomatic or have mild disease.[8–10] Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe postinflammatory complication of SARS-CoV-2 infection that can cause acute myocardial dysfunction, arrhythmias or conduction abnormalities, and coronary artery dilation (Figure).[11–20] Special risk assessment and treatment may be needed for pediatric and young adult patients with preexisting acquired and congenital heart disease, but much remains to be learned.[21] In this scientific statement, we describe what is known about the epidemiology, pathophysiology, clinical presentations, treatment, and outcomes of COVID-19 and MIS-C in the pediatric and young adult populations. We review current knowledge about the health consequences of COVID-19 in children and young adults with congenital and acquired heart disease, consider the public health burden/disparity of this infection, and review COVID-19 vaccine temporally associated with myocarditis in children and young adults.

EPIDEMIOLOGY

COVID-19 has affected all ages, races, and ethnicities around the world. In the early phase of the pandemic, children and young adults were not as frequently or as severely affected by COVID-19 as older adults.[9,22–24] As of February, 24, 2022, in the United States, children <18

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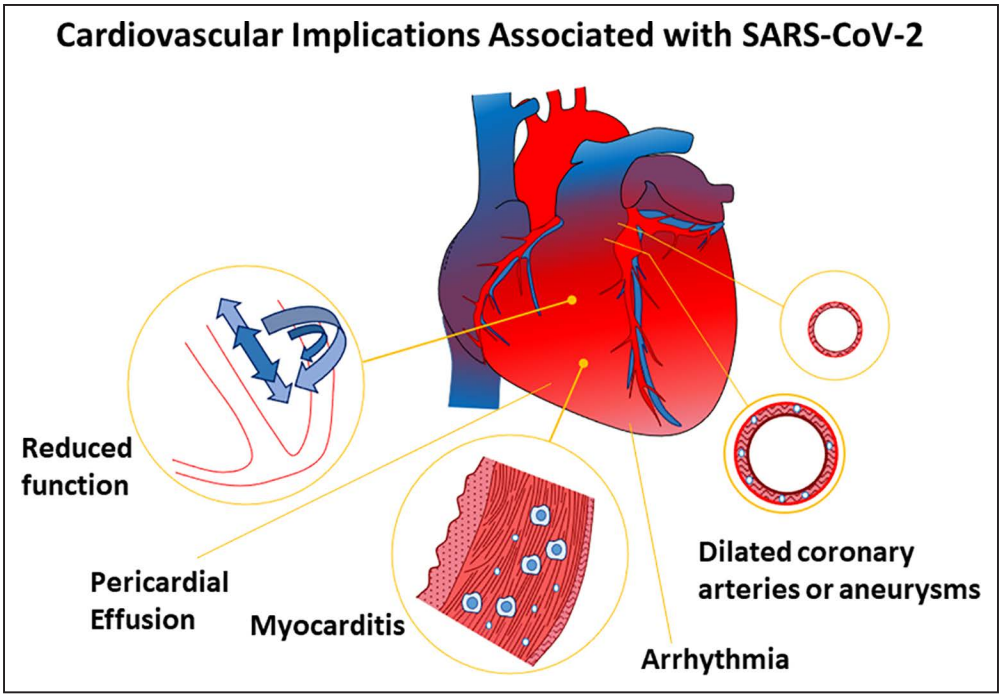

Figure. Cardiovascular implications from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection include reduced function, pericardial effusion, myocarditis, arrhythmia, and dilated coronaries or aneurysms.

years of age have accounted for ≈17.6% of total cases, and ≈0.1% of deaths have occurred in individuals <18 years of age. Similarly, young adults (18–29 years of age) have made up 21.3% of cases and 0.8% of deaths as reported by the Centers for Disease Control and Prevention.[25]

Although the young are relatively spared from clinical disease, some children and young adults appear to be more likely to contract COVID-19 and are at higher risk for experiencing severe illness. The COVID-19 pandemic has disproportionately affected Black and Latino individuals, both in percent of individuals infected and in proportion with severe disease.[25,26] Similar to adults, children with underlying medical conditions such as chronic lung disease or obesity and those who are immune compromised are more likely to be hospitalized, to be admitted to an intensive care unit (ICU), and to die of COVID-19.[8,10,26,26a] There are conflicting reports on the risk of severe COVID-19 in children and young adults with congenital heart disease. Some reports suggest slightly increased risk of severe COVID-19 in association with congenital heart disease,[27–29] whereas other studies demonstrate variable risk for severe disease in patients with congenital heart disease, particularly those with cyanotic congenital heart disease and pulmonary hypertension.[30–32a] Further investigation is needed to better understand the risks associated with congenital heart disease.

Children and some young adults may develop MIS-C, a relatively rare but severe inflammatory syndrome generally occurring 2 to 6 weeks after infection with SARS-CoV-2 that can affect the heart and multiple organ systems.[12,33–35] In the first year of the pandemic, >2600 cases of MIS-C were reported to the Centers for Disease Control and Prevention, at an estimated rate of 1 case of MIS-C per 3164 cases of SARS-CoV-2 infection in children.[36,37] The majority of cases of MIS-C were among children of Hispanic/Latino ethnicity (1 per 2141 cases of SARS-CoV-2 infection) or Black race (1 per 1623 cases of SARS-CoV-2 infection).[37] Even after controlling for underlying rates of COVID-19, MIS-C disproportionately affects children of specific racial and ethnic groups: (1) more non-Hispanic Black children and fewer non-Hispanic White children have MIS-C than expected, and (2) more Hispanic children and fewer non-Hispanic Asian children develop MIS-C than expected on the basis of rates of COVID-19.[38]

PATHOPHYSIOLOGY

The SARS-CoV-2 virus is a large, enveloped, single-stranded RNA virus that binds to the angiotensin-converting enzyme (ACE) 2 (ACE2) receptor on the surface of the host cell with the viral S (spike) protein.[7] Once the viral S protein binds to the ACE2 receptor, the type 2 transmembrane serine protease present in the host cell promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 protein, which then mediates coronavirus entry into the host alveolar epithelial type II cells.[39,40] Proposed mechanisms of cardiovascular involvement in SARS-CoV-2 infection include (1) direct viral invasion of the cardiomyocytes in which ACE2 receptors are highly expressed, resulting in direct cellular damage; (2)

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cardiomyocyte injury attributable to overwhelming immune inflammatory response and cytokine storm; and (3) severe hypoxia, resulting in ischemic myocardial injury.[2,3,7,21,41–43] ACE2 receptors increase with age, suggesting that lower ACE2 levels may in part account for why children have less severe acute SARS-CoV-2 infections.[24] Other studies have suggested that children have fewer ACE2 receptors in the nose, which decreases the ability for SARS-CoV-2 to bind, resulting in less severe disease.[44,45] One study in mice showed a significant increase in the expression profiling for type 2 transmembrane serine protease in adult animals compared with juveniles, which may explain why adults are more susceptible to SARS-CoV-2 infection.[46] Other protective mechanisms proposed in children not developing severe disease include a different cytokine response than in adults and trained immunity related to exposure to live vaccines and frequent viral infections.[47–49] A recent study has demonstrated that nicotine-containing condensates increase ACE2 protein expression, which can increase SARS-CoV-2 infections and severity of disease in children and young adults who frequently vape.[50] It is important to note that ACE inhibitors and angiotensin receptor blockers are safe for use during SARS-CoV-2 infection, and there is no evidence to suggest that treatment with these therapies increases the risk of infection or of developing severe disease.[51]

There are 2 clinical stages of the COVID-19 disease: the acute phase and the hyperinflammatory phase (cytokine storm). The acute phase occurs when SARS-CoV-2 enters lung alveolar epithelial cell type II through the host ACE2 receptor, which results in a proinflammatory response mediated by activation of lung macrophages.[7] Patients are frequently asymptomatic initially and then develop respiratory symptoms, including acute respiratory distress syndrome. As the virus continues to replicate and sparks the hyperinflammatory phase, tissue damage mediated by the innate immune response of the host produces a cytokine storm that is linked to the severity of the illness.[7]

SARS-CoV-2 can cause diffuse alveolar damage with perivascular T-cell infiltration and severe endothelial injury with intracellular virus, which manifests clinically as acute respiratory distress syndrome in acute infection.[52] Patients admitted to the ICU have higher circulating levels of granulocyte-macrophage colony-stimulating factor, interferon γ–induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and tumor necrosis factor-α compared with those who were not admitted to the ICU.[53] Inflamed pulmonary endothelial cells may result in microthrombi formation and contribute to a high incidence of deep venous thrombosis, pulmonary embolism, limb ischemia, ischemic stroke, and myocardial infarction in critically ill patients.[54] Significant elevation in biomarkers associated with myocardial injury, including creatine kinase MB, high-sensitivity cardiac troponin I, and myoglobin, has been seen in the nonsurvivor adult group, with high-sensitivity cardiac troponin I an independent predictor of poor outcome.[55]

Much less is known about the pathophysiology of MIS-C, but it appears that the immune response to MIS-C is different from that of acute infection with the SARS-CoV-2 virus.[56] The pathophysiology of MIS-C is attributed to a hyperimmune response to the virus in a genetically susceptible child.[57] For example, in 1 study, CD8+ T cells were significantly lower in children with MIS-C compared with children with mild SARS-CoV-2 infection.[56] However, despite the significant lymphopenia seen commonly at the time of initial presentation with MIS-C, T-cell activation and proliferation, especially of CD8+ T cells, were found to be more robust in children with MIS-C compared with severely ill adults with COVID-19.[58] In addition, global autoantibody screening found binding of autoantibodies to proteins involved in immune cell signaling and structural proteins in heart and blood vessels.[56] Others have identified a unique T-cell receptor repertoire that is consistent with a superantigen in children with MIS-C.[59] Initial work has not found a T-cell defect in children with MIS-C.[60] Recent RNA sequencing of blood from patients with MIS-C compared with control subjects showed that downregulation of exhausted cytotoxic T cells and natural killer cells may contribute to the pathogenesis of MIS-C.[61]

CLINICAL PRESENTATION

Acute SARS-CoV-2 Infection

Acute SARS-CoV-2 infection is characterized by an initial phase that either is asymptomatic or involves respiratory or gastrointestinal symptoms that is sometimes followed by a hyperinflammatory phase (cytokine storm) as the virus continues to replicate. Fortunately, most children and young adults infected with SARS-CoV-2 have mild disease, with a significant proportion (8%–19%) being completely asymptomatic.[9,23] For children presenting with symptoms, the 2 most common symptoms in the acute phase are fever and cough.[9,62] Unlike adults, loss of taste or smell is less common in children, occurring in <1%.[63] Although rare, severe neurological complications such as encephalitis, seizures, and strokes and thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been described in children and young adults.[11,64–66]

Cardiovascular manifestations of acute COVID-19 infection in children are uncommon. Case reports and small series have described cardiogenic shock, myocarditis, pericarditis, and arrhythmias.[67–70] Arrhythmias have included ventricular tachycardia and atrial tachycardia, as well as first-degree atrioventricular block.[15,71] Although arrhythmias are generally nonsustained and self-resolve without need for treatment, prophylactic antiarrhythmics

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have been administered in some cases,[15] and death caused by recurrent ventricular tachycardia in an adolescent with hypertrophic cardiomyopathy has been described.[72] Elevations of troponin, electrocardiographic abnormalities, including ST-segment changes, and delayed gadolinium enhancement on cardiac magnetic resonance imaging have been seen in those with myocardial involvement.[73–75] Although death is rare, both sudden cardiac death and death after intensive medical and supportive therapies, including extracorporeal membrane oxygenation (ECMO), have occurred in children with severe myocardial involvement.[76,77] Initiation of ECMO for the treatment of acute COVID-19– or MIS-C–related severe cardiopulmonary failure is reasonable, with indications, patient selection, and clinical management based on conventional guidelines.[77] In a large retrospective pediatric case series of SARS-CoV-2–associated deaths in individuals <21 years of age, the median age at death was 17 years (interquartile range, 8.5–19 years; range, 1 month–20 years), 63% were male, 28% were non-Hispanic Black, and 46% were Hispanic.[78] Of those who died, 86% had a comorbid condition, with obesity (42%) and asthma (29%) being the most common.[78]

A systematic review of the pediatric literature demonstrated that 108 of 5686 children (1.9%) required intensive care and mechanical ventilation because of acute SARS-CoV-2 infection.[29] In this review, of those with severe illness and mechanical ventilation for whom detailed medical information was available, 75% had comorbidities, including various forms of congenital heart disease or cardiomyopathy (21%), obesity (15%), neurological disorders (10%), asthma (10%), and hypertension (2%).[29] Other less common comorbidities associated with severe acute SARS-CoV-2 infection include immunodeficiencies, cancer, genetic syndromes, diabetes, and a history of prematurity. Death occurred in 17 (which is 16% of the severely ill children and 0.3% of all infected children included in this review), with 75% having at least 1 comorbid condition, although none of those who died had congenital heart disease or cardiomyopathy. In summary, although children with comorbidities are at increased risk for symptomatic SARS-CoV-2 infection compared with healthy children, cardiovascular complications, severe illness, and death are uncommon.

Multisystem Inflammatory Syndrome in Children

A systematic review including >900 children described the presenting symptoms of MIS-C as fever (99%), gastrointestinal symptoms (87%; vomiting or diarrhea), abdominal pain (70%), nonpurulent conjunctivitis (57%), rash (59%), and oral mucosal changes (42%; Table).[14] Neurological symptoms at presentation can include headache (29%) and altered mental status or confusion (2%).[34] The median age range at diagnosis of MIS-C was 8 to 9 years; 57% to 59% were male; 35% to 37% were Hispanic and Black; and 25% to 31% had at least 1 comorbid condition (eg, obesity, asthma, other chronic lung disease).[14]

The differential diagnosis of MIS-C includes Kawasaki disease, adenovirus infection, bacterial infectious diseases (eg, enteritis, sepsis, or toxic shock syndrome), autoimmune and autoinflammatory disorders, and acute appendicitis.[80,81] Although at present there is significant practice variation, evaluation for MIS-C often includes a careful history and physical examination with documentation of duration of fever; laboratory evaluation, including SARS-CoV-2 polymerase chain reaction or serologies; C-reactive protein; ferritin; BNP (brain natriuretic peptide) or NT-proBNP (N-terminal pro-B-type natriuretic peptide); troponin; a complete metabolic panel; a complete blood count; a complete 2-dimensional echocardiogram with assessment of cardiac function and evaluation of the coronary arteries; and an ECG.[82] Additional studies such as blood cultures, chest radiographs, lumbar puncture, or other imaging studies should be performed as clinically indicated. As many as 50% of children with MIS-C have myocardial involvement, including decreased left ventricular function (defined as an ejection fraction <55%) in 28% to 55% of patients, coronary artery dilation or aneurysms in 12% to 21%, myocarditis in 17% to 18%, elevated troponin and BNP or NT-proBNP, or pericardial effusion in 23% of the patients.[14,35,57,80] Arrhythmias, heart block, and other electrocardiographic abnormalities (eg, ST-segment changes, QTc prolongation, and premature atrial and ventricular contractions) are less common findings but have been described.[20,83,84] Acute-phase reactants, including C-reactive protein, D-dimer, ferritin, and fibrinogen, can be significantly elevated in MIS-C.[14,35] Patients with MIS-C have a higher neutrophil/lymphocyte ratio and lower platelet counts than those with non–MIS-C febrile illnesses.[35,80]

Fortunately, the outcome of MIS-C is generally very good, with resolution of inflammation and cardiovascular abnormalities within 1 to 4 weeks of diagnosis.[85,86] However, some series report progression of coronary artery aneurysms after discharge, highlighting the potential for long-term complications.[13] Death resulting from MIS-C is rare, with a mortality rate of 1.4% to 1.9%.[14,35] Compared with children and young adults who died of acute SARS-CoV-2 infection, most of the fatalities from MIS-C were in previously healthy individuals without comorbidities.[78] Structured follow-up of patients with MIS-C because of concern about progression of cardiac complications and an unclear long-term prognosis is suggested. One study proposed that outpatient follow-up intervals include 1 to 2 weeks, 4 to 6 weeks, 4 to 6 months, and 10 to 12 months after discharge with repeat laboratory values, ECG, echocardiograms, Holter monitoring, or exercise stress tests, depending on the patients' clinical status at discharge and subsequent follow-up.[13] Long-term prospective data collection of patients with MIS-C for the next 5 years is underway in the MUSIC study (Long Term

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Table. Diagnostic Criteria for Acute COVID-19, MIS-C, and Kawasaki Disease

	Acute COVID-19[24]	CDC MIS-C	WHO MIS-C	Complete KD[79]	Incomplete KD[79]
Age	Any age	<21 y	0–19 y	Usually 2–5 y of age	<18 y
Fever	≥38.0°C	≥38.0°C for ≥24 h or subjective fever	Fever ≥3 d	Fever ≥5 d	Fever ≥5 d or infants with fever ≥7 d
Evidence of inflammation	Yes	≥1 Laboratory evidence of inflammation: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, neutrophils, lymphopenia, hypoalbuminemia	≥1 Laboratory evidence of inflammation: elevated CRP, ESR, or procalcitonin	Inflammation is present with elevated CRP and ESR	>1 Marker of inflammation: elevated CRP or ESR AND 3 or more of the following: anemia, thrombocytosis after the 7th d of fever, hypoalbuminemia, leukocytosis, transaminitis, sterile pyuria
		AND	AND	AND	
Multisystem involvement	Shortness of breath, cough, running nose May have thromboembolic events and respiratory failure	≥2 Organ systems involved: cardiac, renal, pulmonary, hematological, gastrointestinal, dermatological, or neurological	≥2 of the following: mucocutaneous inflammation (rash, bilateral, nonpurulent conjunctivitis, or oral, hands, or feet edema and redness); hypotension or shock; cardiac involvement; coagulopathy (abnormal PT, PTT, or elevated D-dimer); or acute gastrointestinal illness (diarrhea, emesis, or pain)	≥4 of 5 of the following: inflamed lips, strawberry tongue, or oral/pharyngeal mucosa; bilateral, nonpurulent conjunctivitis; edema and redness of the hands and feet; or cervical lymphadenopathy of ≥1.5 cm	
Cardiac abnormalities indicative of involvement	May have evidence of pericarditis or myocarditis	Abnormal biomarkers: elevated troponin or BNP or NT-pro-BNP Electrocardiographic changes: conduction block, ST-segment elevation, myocardial ischemia, low-voltage echocardiographic findings: *z* score ≥2 in any of the proximal coronary arteries Ventricular dysfunction (right, left, or both), mitral regurgitation, pericardial effusion	Same as CDC MIS-C	Cardiac involvement defined as the following: *z* score of LAD or RCA ≥2.5; coronary artery aneurysm; or ≥3 features of decreased LV function, mitral regurgitation, pericardial effusion, or LAD or RCA *z* score 2–2.5	Same as complete KD; abnormal echocardiogram is diagnostic of incomplete KD even in the absence of multiple laboratory findings
		AND	AND	AND	AND
Additional required features	Positive for SARS-CoV-2 infection by RT-PCR	Positive for SARS-CoV-2 infection by RT-PCR, serology, or antigen test or exposure within 4 wk to a suspected or confirmed COVID-19 case	Positive for SARS-CoV-2 infection by RT-PCR, serology, or antigen test or likely exposure to COVID-19 case	No alternative pathology or diagnosis	No alternative pathology or diagnosis
		AND	AND		
		No alternative pathology or diagnosis	No alternative pathology or diagnosis		

BNP indicates brain natriuretic peptide; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; KD, Kawasaki disease; LAD, left anterior descending artery; LDH, lactate dehydrogenase; LV, left ventricular; MIS-C, multisystem inflammatory syndrome in children; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; RCA, right coronary artery; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; and WHO, World Health Organization.

Outcomes After Multisystem Inflammatory Syndrome in Children) funded by the National Heart, Lung, and Blood Institute.[87]

TREATMENT

Management of Primary SARS-CoV-2 Infection

Because COVID-19 often causes a mild respiratory illness in children, treatment is mostly supportive. Monoclonal antibody therapy is recommended for outpatient management of adults with mild to moderate disease who are considered to be at high risk for progression.[88] The FDA approved of monoclonal antibodies for treatment and post-exposure prevention of COVID-19 to younger pediatric patients including newborns in December 2021.[89] Patients with dyspnea should be evaluated by a health care professional, and those with moderate or severe disease, comorbid chronic health conditions, or unclear trajectory may need to be monitored and treated in a hospitalized setting.[90] In hospitalized patients, mild hypoxia may be manageable with close monitoring and administration of supplemental oxygen alone. With progressive respiratory distress, refractory hypoxemia, or carbon dioxide retention, transfer to an ICU setting for administration of high-flow nasal oxygen, noninvasive

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ventilation, or intubation for mechanical ventilation may be necessary.[91] Although data are limited in pediatrics, prone positioning and ECMO have been used for severe pneumonia and acute respiratory distress syndrome.[91] In addition to respiratory management, critically ill patients with COVID-19 must be monitored and treated for myocarditis, hypercoagulability and associated thrombotic events, bacterial superinfection and sepsis, kidney dysfunction, and neurological dysfunction.[91]

Antiviral and immunomodulatory therapy may be indicated in the setting of severe disease. There are currently no specific COVID-19 antiviral therapies. Repurposing of existing antiviral, antibacterial, and antimalarial therapies has been explored in adult populations with mixed results.[92] Remdesivir is currently the only drug approved by the US Food and Drug Administration for the treatment of hospitalized children ≥12 years of age who have risk factors for severe disease and have an emergency need for or require supplemental oxygen.[88,93] Remdesivir is also recommended for hospitalized children ≥16 years of age who have an emergency or increasing need for supplemental oxygen even in the absence of risk factors and can be considered for other hospitalized children of all ages with COVID-19 who have an emergency or increasing need for supplemental oxygen in consultation with a pediatric infectious disease specialist.[88,93] Remdesivir should be given early in the clinical course because it may be less effective in severe disease.[94] For patients who progress to severe disease (mechanical ventilation or ECMO), the addition of dexamethasone has been shown to reduce mortality in adult patients, presumably by modulating the inflammatory response.[95] Dexamethasone is recommended in children who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or ECMO.[88,96] Dexamethasone is not recommended for the treatment of mild to moderate COVID-19 disease in children.[96] Although a number of additional agents are being investigated and used in adults, there are currently insufficient data to recommend routine use of other specific antimicrobial or immunomodulatory agents in the treatment of primary SARS-CoV-2 infection in pediatric patients.[88] Specifically, the US Food and Drug Administration's Emergency Use Authorization for the use of the antimalarials chloroquine and hydroxychloroquine in the treatment of patients with COVID-19 was revoked in June 2020, with a lack of evidence and concern for treatment-related serious cardiac adverse events cited as reasons.[97] Similarly, the safety and efficacy of convalescent plasma have not been demonstrated in pediatric patients with COVID-19, and there is insufficient evidence to recommend its use in children.[88]

Management of MIS-C

Treatment of MIS-C focuses on modulation of the postinfectious inflammatory state and supportive care. Supportive treatment of heart failure and vasoplegic shock often requires aggressive management in an ICU for administration of inotropes and vasoactive medications. In a review of 953 patients with MIS-C, inotropic support was needed in 73.3% of patient with hypotension or ventricular dysfunction.[98] Respiratory support with noninvasive or mechanical ventilation was used in 3% to 4% of patients (up to 30% in other studies), and some required ECMO.[14,98] Although robust clinical trial data are lacking, the first-line treatment for MIS-C is typically intravenous immunoglobulin (IVIG).[11,13,14,17,18,33–35,82] In all reviews and case series of reported MIS-C, 70% to 80% of patients received IVIG, and the majority improved and had recovery of cardiac function.[13,14,17,18,33–35,82] Patients with poor ventricular function may need to have IVIG in divided doses in order to tolerate the fluid load.[17] Patients with coronary artery dilation (z score >2) or left ventricular dysfunction have been treated with infliximab (tumor necrosis factor-α antagonist), glucocorticoids, or anakinra (interleukin-1 receptor antagonist).[14,82,99,100] These immunomodulators also have been used in patients with severe cytokine release syndrome.[82] A retrospective study of 181 children with suspected MIS-C conducted by the French COVID-19 Pediatric Inflammation Consortium demonstrated that treatment with combined IVIG and methylprednisolone versus IVIG alone was associated with a more favorable fever course.[101] A second study of >500 patients with MIS-C by the Overcoming COVID-19 Investigators evaluating initial therapy with IVIG versus IVIG plus steroids showed lower risk of new or persistent cardiovascular dysfunction and less use of adjunctive therapy, but the length of ICU stay and fever duration did not differ between the 2 groups.[102] BATS (Best Available Treatment Study), which evaluated IVIG versus IVIG plus steroids versus steroids alone, did not show any difference between the 3 groups in the primary composite outcome of inotropic support or mechanical ventilation by day 2 or death.[103] BATS also showed that there was no reduction in disease severity by day 2 or reduced use of adjunctive therapy between the groups.[103] A single-center study of initial therapy with IVIG plus infliximab versus IVIG alone demonstrated decreased length of ICU stay, decreased development of left ventricular dysfunction, decreased need for additional therapy, and more rapid decline of inflammation.[100] The MISTIC comparative-effectiveness study (Multisystem Inflammatory Syndrome Therapies in Children) is an ongoing randomized prospective trial that began in December 2020 and is evaluating the addition of infliximab, steroids, or anakinra after initial treatment with IVIG.[79] Antiplatelet therapy with low-dose aspirin is considered in patients with coronary artery involvement, and anticoagulation is added, depending on the degree of coronary artery dilation.[79] The risk of thrombotic events in association with MIS-C remains unresolved, so although anticoagulation therapy has been described, there is

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wide practice variation at present, and evaluation of risk versus benefit in individual patients is encouraged.[17,82]

PROGNOSIS AND SPORTS CLEARANCE

Long-term outcome data after SARS-CoV-2 infection are not yet available, but midterm data in children and youth are encouraging.[104,105] Early reports raised concern for significant cardiac complications after infection in youth; however, subsequent review of outcomes in young athletes indicates that a majority have had no adverse cardiac sequalae after asymptomatic or mild infection.[106–109] Comprehensive systematic screening, including cardiac enzyme levels, ECG, echocardiogram, stress echocardiogram, and magnetic resonance imaging, in athletes 17 to 41 years of age was reassuring, with minimal indications of persistent or significant myocarditis or pericarditis.[107,108] However, there are few data on cardiovascular sequelae in youth after moderate to severe infection or MIS-C, and there is concern that these patients could have a higher incidence of long-term cardiovascular sequelae.[13,110] A number of algorithms have been developed to guide screening; more long-term data are needed to refine recommendations.

Available data suggest that it is safe to allow asymptomatic youth and those with mild infection (upper respiratory infection symptoms and <4 days of fever) to return to sports after recovery from SARS-CoV-2 infection. In contrast, until better outcome data are available, it is reasonable to consider screening youth with greater than mild SARS-CoV-2 infections or MIS-C with cardiovascular testing, including but not limited to cardiac enzyme levels, ECG, and echocardiogram, before return to sports.[108,109,111] A gradual return to play can be considered after infection.[112] If significant abnormalities are present on initial cardiac tests, stress testing, Holter monitoring, and cardiac magnetic resonance imaging can be considered to identify persistent inflammation or scarring from COVID-19–related myocarditis or pericarditis. Patients who have acute myocarditis from acute COVID-19 or MIS-C are restricted from exercise for 3 to 6 months, similar to restrictions after other viral myocarditis.[113] For youth with symptoms that may indicate cardiovascular pathology after SARS-CoV-2 infection of any severity, cardiovascular consultation is recommended before a gradual return to play is allowed.[111]

SPECIAL CONSIDERATIONS IN PEDIATRIC AND ADULT CONGENITAL HEART DISEASE

Congenital Heart Disease

Congenital heart disease was initially thought to confer higher risk for more severe SARS-CoV-2 infections because certain subtypes of congenital heart disease have a higher incidence of congestive heart failure and cardiac dysrhythmias. Because of the heterogeneity of congenital heart disease, however, it has been difficult to determine risk profiles for specific subtypes. In addition, the risk profile of pediatric versus adult patients with congenital heart disease is likely to be variable as a result of the diversity of risk factors such as age and associated morbidities, clouding our understanding of congenital heart disease–associated risk for severe COVID-19.[27,32]

Several guidelines have been published proposing risk stratification profiles for severe COVID-19 that are based on underlying congenital heart disease.[21,28,114–116] Children with congenital heart disease appear to have low infection and mortality rates from acute SARS-CoV-2 infection.[30,117,118] However, the presence of an underlying genetic syndrome such as trisomy 21 appears to convey an increased risk of severe infection.[30,119] A multicenter study from 58 adult congenital heart disease centers showed that COVID-19 mortality was similar to that of the general adult population.[32] Of 1044 infected patients with adult congenital heart disease, there were 24 COVID-19–related deaths (2.3%). Data have shown that worse physiological stage, as defined by the American College of Cardiology/American Heart Association guidelines for the management of adults with congenital heart disease, not anatomic complexity, confers higher risk of death and serious infection.[30,32] Additional risk was seen in male patients and in patients with a history of diabetes, cyanosis, pulmonary hypertension, renal insufficiency, Eisenmenger syndrome, or previous hospitalization for heart failure.[32]

Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) has been categorized as an underlying condition that confers higher risk for serious SARS-CoV-2 infection.[119] There are several mechanisms by which COVID-19 can worsen underlying PAH. Pneumonia with resultant hypoxia and hypercapnic vasoconstriction is a potential mechanism for worsening PAH.[120] Accumulation of inflammatory cells in the endothelium with resultant cytokine release results in further cell death and inflammation, potentially worsening underlying PAH.[121] A survey of 58 PAH centers showed an incidence of 2.9 cases of COVID-19 infection per 1000 patients.[122] Hospitalization was markedly higher than for the general population at 30% of cases, and mortality occurred in 12% of cases.[122] Although this study included 7 pediatric centers, there was not a breakdown of the pediatric patients with PAH and COVID-19.[122] Some data on pediatric patients with idiopathic PAH suggest that rates of infection likely mirror the overall pediatric population.[123]

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Pediatric Heart Failure and Heart Transplant Recipients

The implications of acute SARS-CoV-2 infection in pediatric and young adult patients with heart failure and recipients of heart transplantation are incompletely understood. Younger age and the low number of comorbidities in pediatric and young adult patients who otherwise are considered high risk for infectious complications likely contribute to the less severe implications of SARS-CoV-2 infections seen thus far compared with their older adult counterparts.[124] A multicenter review reported 26 pediatric solid-organ transplant recipients who contracted SARS-CoV-2 infection, including 6 heart transplant recipients.[125] Of the 6 heart recipients, 2 were hospitalized; neither required supplemental oxygen or a change in their immunosuppression regimen, and both were discharged to home. In fact, all of the solid-organ recipients with SARS-CoV-2 infection in this series recovered completely, suggesting no evidence thus far of higher risk compared with immunocompetent peers. However, adult studies have shown higher risk in solid-organ transplant recipients.[126] More evidence is needed in children with solid-organ transplantation, but caution should be taken with this population given immunosuppression and the unknown risk of SARS-CoV-2 infection on the graft. The association of SARS-CoV-2 infection and future acute graft rejection in pediatric heart transplant recipients is currently unknown. However, similar to other viral infections, allosensitization after SARS-CoV-2 infection has been described, so careful follow-up of these vulnerable children is reasonable.[127] An interesting point is that tacrolimus, a common maintenance immunosuppressive therapy in pediatric transplant recipients, has in vitro activity against SARS-CoV-2 replication.[128] This information, along with observational studies of SARS-CoV-2–infected solid-organ transplant recipients treated with tacrolimus, suggests that continued use of tacrolimus in this setting may be reasonable.[129]

PUBLIC HEALTH BURDEN

The substantial public health burden of the COVID-19 pandemic includes not only direct mortality and morbidity but also delays in routine care, elective procedures, and the negative effects of stay-at-home orders on the general pediatric population and individuals with congenital heart disease. Routine care was dramatically curtailed in early months to free up health care resources for direct care of children and adults infected with SARS-CoV-2 and to protect patients, families, and health care professional teams from virus transmission. These changes to ambulatory care resulted in delays in routine visits and missed screenings.[130] Prenatal fetal screening and diagnosis with genetic and structural anomalies were adversely affected by the pandemic.[131] Routine vaccination rates temporarily declined in the Unites States and elsewhere, particularly in children >24 months of age.[132] Ambulatory volume declined substantially. One study showed a 49% decrease compared with the prior year despite the rapid adoption of telehealth, which was used for 61% of ambulatory visits in 1 series.[133] Visits to the emergency room decreased significantly, and hospitalizations dropped by as much as 83%, attributable to cancellation of routine procedures and a decline in communicable diseases as a result of social distancing.[134,135] Information continued to emerge about the impact of these reductions in care, but some negative health impact is likely.[136,137]

The pandemic also disrupted routine care of those with congenital heart disease. A survey of parents of children with congenital heart disease and individuals with adult congenital heart disease found that 38% reported delays in scheduled cardiac surgeries and 46% had postponed clinic visits,[138] causing psychological stress among patients and their families.[138] In addition to modifications to care delivery put in place by clinics and hospitals, patients and families were fearful of seeking care because of the risk of exposure to SARS-CoV-2, possibly resulting in preventable cardiac complications.[139] Negative effects on congenital heart disease care were seen across the globe. Closing of borders affected access to congenital heart disease care in low- and middle-income countries,[140,141] including mission-based delivery of surgical care, accentuating the disparities in health care exposed by the COVID-19 pandemic.[142]

Social distancing and lockdowns had substantial negative effects on youth, beyond the direct impact of the virus and its effect on the provision of health care services. School closures and home confinement increased the risk for emotional distress, domestic abuse, and social isolation.[143] Efforts are ongoing to describe the extent of collateral damage, but learning undoubtably suffered. Early predictions[144] described fears about the impact of school closings on access to healthy food and education, a key counteracting force for poverty and inequality. School closings may have additional negative impacts on health in the short and long terms.[145,146] One meta-analysis of the mental health symptoms measured during the COVID-19 pandemic showed the 22.6% to 43.7% of youth experienced depressive symptoms and 18.9% to 37.4% reported anxiety symptoms.[147] Half of college students experienced moderate to severe depression; 38% had moderate to severe anxiety; and 71% experienced a rise in stress related to the pandemic. A concerning finding was that 18% described suicidal thoughts.[148] Mental health disorders were already at record high levels among youth, and the data are not definitive with regard to causality, although national prevalence rates of diagnosed disorders are substantially lower than reported in these studies (3.2% and 7.1% of children 3–17 years of age have depression and anxiety, respectively).[149] At least 1 longitudinal study of 571 male youth showed that 32% experienced a worsening in mood and 32% had increased anxiety.[150] Compared with 2019, the proportion of mental health–related emergency

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department visits for children 5 to 11 and 12 to 17 years of age increased by ≈24% and 31%, respectively.[151]

An additional unintended consequence of stay-at-home orders was a rise in behaviors adversely affecting cardiovascular health such as increased inactivity (screen time), plummeting of physical activity, lack of access to healthy foods, and resultant weight gain.[152–154] Small studies of children and adults with obesity before the pandemic showed rising body mass index, fatty liver, and hyperlipidemia.[155–157] These effects, like the effects on learning, mental health, and socialization, may leave a permanent mark on the youth of today.

HEALTH DISPARITIES

The COVID-19 pandemic has accentuated known disparities in health care delivery and outcomes related to social determinants of health.[158–162] Children experienced worsening disparities because of their dependence on adult caregivers.[163] Factors related to exposure, access to care, and the disproportionate burden of COVID-19–related morbidity and mortality exacerbated the existing social and economic disparities experienced by marginalized groups.

Exposure at Work and Home

Overrepresentation of Black and Hispanic adults in essential industries reduces their ability to practice social distancing or to leverage work-from-home or paid-leave policies, thereby increasing the risk of repeated exposure.[163] Workers without paid sick leave may be more likely to continue to work despite illness stay-at-home recommendations, potentially increasing workplace exposure and subsequent spread. The likelihood of living in a multigenerational household, more common in underrepresented racial and ethnic groups, also increases the risk for household exposures because separation from others may be more difficult.[164]

Access to Care

COVID-19 is exacerbating existing disparities attributable to barriers that include inadequate access to testing, lack of transportation, and lack of insurance coverage.[161] It is anticipated that the disparities arising from the lack of health insurance also will have a major impact on health care use and outcomes.[159] Motivated in part by the pandemic, the implementation of telehealth has moved the delivery of health care beyond the traditional face-to-face model, which allows improved accessibility despite transportation or missed work concerns.[161,165] However, telehealth relies on reliable internet connections, which are less available to those with lower socioeconomic status. It remains to be shown whether the same quality of cardiovascular care can be delivered via telehealth and whether cardiovascular health outcomes overall are affected positively or negatively by this shift.[166]

Implicit Bias

Long-standing structural inequities and implicit biases are common within the health care system and contribute to disparities in treatment decisions, patient mistrust, and gaps in patient–health care professional communication.[160,165] The additional strain on clinician resources, staff, and supplies created by COVID-19 may exacerbate clinicians' susceptibility to implicit bias and contribute to health disparities.[160]

Outcomes of Different Populations

The effects of COVID-19 on the health of underrepresented racial and ethnic groups are still emerging. Current data suggest a disproportionate burden of illness and death among non-Hispanic Black, Native Hawaiian, Pacific Islander, American Indian, Alaska Native, and Hispanic individuals.[167] These inequities are thought to be related to both the unequal distribution of concomitant comorbidities and social determinants of health in these vulnerable populations.

VACCINE-ASSOCIATED MYOCARDITIS

Vaccination is underway to prevent COVID-19 in those ≥5 years of age. Research on the safety of vaccination in infants and young children is in progress. Myocarditis and pericarditis, presenting with chest pain and high troponin levels typically 2 to 6 days after receipt of mRNA COVID-19 vaccine in young people, have been reported to the Vaccine Adverse Event Reporting System.[168,169] In a series of 63 patients ≤21 years of age with myocarditis temporally associated with the COVID-19 vaccine, the mean age was 15.6 years, 92% were male, all had an elevated troponin, 7% had significant arrhythmias, 14% had decreased left ventricular systolic function (ejection fraction, 45%–54%), and 88% had evidence of myocarditis on cardiac magnetic resonance imaging.[170] In this cohort, at a mean follow-up of 35 days, 86% of patients had resolution of symptoms and normalization of function; follow-up was not available in the remaining 14%.[170] Treatment is largely supportive and includes primarily pain management with oral anti-inflammatory medications, although IVIG, steroids, and colchicine have been used.[170–172] The mechanisms of myocarditis and pericarditis associated with mRNA COVID-19 vaccines are unknown at this time; the reasons for male predominance in these cases are also unknown.[173] The benefit of COVID-19 vaccine outweighs the risks of rare myocarditis/pericarditis temporally associated with COVID-19 vaccine: Per 1 million doses of COVID-19 vaccine in male individuals 12 to 29 years of age (the highest-risk group for vaccine-associated myocarditis), 11 000 COVID-19 cases, 560 hospitalizations, and 6 deaths would be prevented, whereas 39 to 47 cases of myocarditis would be expected.[174] A study demonstrated that receipt of 2 doses

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of mRNA COVID-19 vaccine is highly effective in preventing MIS-C in the 12- to 18-year-old age group: the estimated effectiveness against MIS-C was 91% (95% CI=78%-97%).[175] Thus, COVID-19 vaccination is still recommended to curb this pandemic, but active efforts are underway to investigate potential long-term effects of myocarditis associated with COVID-19 vaccination.[176]

FUTURE

COVID-19 is still a relatively new disease, and our understanding of its effects, as well as the effects of the postinflammatory condition MIS-C, on the general pediatric population and on children and adolescents with acquired and congenital heart disease is evolving. We need to better understand the mechanisms, optimal treatment approach, and long-term outcomes of MIS-C. The development of novel antiviral therapies needs to be tested in children in clinical trials. Investigations focused on the long-term outcomes are needed for children with and without acquired and congenital heart disease who have had SARS-CoV-2 infection. The consequences of long COVID-19 and the impact of this disease on the heart have yet to be elucidated in children and young adults.

CONCLUSIONS

SARS-CoV-2 infection continues to infect patients worldwide, with variants circulating in different parts of the world. We have much to learn about the pathology of this disease but have gained some ground on the treatment of COVID-19 and management of children with MIS-C. The long-term cardiovascular manifestations of COVID-19 in children require continued clinical research trials.

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ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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