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Cardiology/CT Surgery (K Gist, Section Editor)

Management of Multisystem Inflammatory Syndrome in Children Associated with COVID-19 Infection

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Abstract

Purpose of review The purpose of this review is to summarize what is known about multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 infection.
Recent findings The timing of presentation and features of diagnosis are described. Cardiac involvement is common and is the focus of this review. Arrhythmias, heart block, acute heart failure, shock, cardiac dysfunction, and coronary dilation have all been reported. Therapies used to treat children with this hyperinflammation syndrome include supportive care and agents that modulate the immune system. Therapies commonly described include intravenous immunoglobulin, steroids, and cytokine-directed agents, particularly tumor necrosis factor-alpha blockade and interleukin receptor blockade. The threshold for diagnosing coronary involvement in MIS-C is coronary artery dimensions indexed to body surface that exceed the normative values (Z score >2). Those hospitalized with MIS-C are evaluated by electrocardiogram and echocardiogram; outpatient assessment by a cardiologist is indicated prior to sports clearance.
Summary The prognosis of treated MIS-C patients is good. Future work is needed to understand the scope of cardiac involvement associated with acute COVID-19 and MIS-C in children and to define the optimal therapeutic targets for these distinct entities.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2), was first reported in Wuhan, China, in December 2019, and was declared a global pandemic on March 11, 2020. One year since the declaration of the pandemic, it has affected 122.9 million people worldwide (2.7 million deaths) and 29 million people in the USA (536,781 death) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). The exponential rise in the number of COVID-19 patients has overwhelmed the health-care system worldwide and caused unprecedented effects on public health. Cardiovascular complications from COVID-19 in adults have been reported to induce myocardial injury, arrhythmias, acute coronary syndrome, venous thromboembolism, and pulmonary artery embolus [1–8•]. Infection in pediatric and adolescent patients presents in asymptomatic or milder disease compared to adults [9–13]. However, early in the pandemic, pediatric health-care providers noted a rise in multisystem inflammatory illness in children with a history of COVID-19 infection or known exposure. The first reports of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 emerged in May 2020. As of January 2021, the Center for Disease Control has tracked over 2600 cases and 33 deaths attributed to MIS-C in the USA (https://www.cdc.gov/mis-c/index.html). Cardiac involvement is a common feature of MIS-C associated with COVID-19 infection and includes acute heart failure, cardiac dysfunction, abnormal cardiac biomarkers, and coronary artery abnormalities [14, 15•, 16, 17, 18, 19•]. In this statement, we describe the pathophysiology, clinical presentations, and treatment of COVID-19-associated MIS-C.

Pathophysiology

The SARS-CoV 2 virus is a member of the coronavirus and binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of the host cell using the viral S (spike) protein. In early infection, the SARS-CoV2 targets nasal and bronchial epithelial cells and pneumocytes [20]. After the viral S protein binds to the ACE2 receptor, the type 2 transmembrane serine protease (TMPRSS2), present in the host cell, promotes viral uptake by cleaving ACE2 and activating the SARS-CoV2 protein which then mediates coronavirus entry into the host alveolar epithelial type II cells [20, 21, 22••]. Profound lymphopenia occurs when SARS-CoV 2 infects and kills T lymphocytes. In later stages of the infection, viral replication accelerates, and epithelial-endothelial barrier is compromised. SARS-CoV 2 infection also infects the pulmonary capillary endothelial cells which then accentuates the inflammatory response, triggering an influx of monocytes and neutrophils [22••]. Pulmonary edema ensues, and acute respiratory distress syndrome (ARDS) develops. In severe COVID-19 infection, activation of coagulation and consumption of clotting factors occur. Inflamed pulmonary endothelial cells may result in microthrombi formation and contribute to the high incidence of deep venous thrombosis, pulmonary embolism, limb ischemia, ischemic stroke, and myocardial infarction in critically ill patients [23, 24]. Viral sepsis can develop with dysregulation of the host immune response to the infection and can contribute to multiorgan failure.

There are two clinical stages of the disease: the acute phase and hyperinflammatory phase (cytokine storm). The acute phase occurs when SARS-CoV2 enters lung alveolar epithelial cell type II through the host ACE2 receptor which results in a pro-inflammatory response mediated by activation of lung macrophages [25–27]. Patients are frequently asymptomatic

initially and then develop ARDS as virus continue to replicate. The hyperinflammatory phase occurs when body tissue damage is mediated by host's innate immunity by producing cytokine storm that resemble macrophage activation syndrome [28, 29]. Patients with cytokine storm can damage cardiomyocytes and present with multisystem inflammatory syndrome. Initially reported in children as MIS-C, it is now recognized to occur in adults (MIS-A) [30]. MIS-A is identified using a similar case definition and excluding adults with severe respiratory illness to distinguish these cases from adults with severe COVID-19. In adults, arrhythmias, elevated cardiac biomarkers, and right or left ventricular dysfunction are most described. However, cardiac endotheliitis and multisystem vasculitis were found at autopsy of a 31-year-old female with MIS-A after COVID-19 [31]. This latter description of small artery inflammation is a common feature of MIS-C. The cardiovascular complications in children include arrhythmias, conduction abnormalities, elevated troponin and natriuretic peptides, cardiac dysfunction including acute heart failure and shock, pericardial effusion, and coronary artery dilation, with some overlapping clinical features similar to Kawasaki disease (KD) [13, 15•, 16, 32]. While most cases of MIS-C present 3–4 weeks after initial COVID-19 infection, there is one well-defined case of MIS-C with coronary involvement reported to date which occurred 16 weeks after the onset of COVID-19 [33].

Clinical presentation

MIS-C is a syndrome that results from an abnormal immune response to the SARS-CoV 2 virus with some similarities to KD, macrophage activation syndrome, or cytokine storm. MIS-C has been diagnosed 2–16 weeks after the COVID-19 infection, but the typical time course is 3–4 weeks after acute COVID-19 illness [34, 35•, 36•]. Table 1 compares the MIS-C case definitions and the diagnostic criteria for complete and incomplete KD. A recent systemic review of MIS-C in 440 patients showed that median age of patients ranged from 7.3 to 10 years where 59% of all patients were male [17]. Thirteen to 69% of the patients were tested positive for SARS-CoV 2 PCR and for serology from 75 to 100% [17]. Patients had high prevalence of gastrointestinal (87%), dermatologic/mucocutaneous (73%), and cardiovascular (71%) symptoms [17]. MIS-C affects older children and adolescents, whereas KD affects infants and young children. Black and Hispanic children appear to be disproportionally affected in MIS-C, whereas Asians have a higher incidence in Kawasaki disease [17]. Gastrointestinal symptoms are very common in MIS-C with myocardial dysfunction and shock occurring more commonly in MIS-C patients compared to KD patients. Inflammatory markers such as c-reactive protein, ferritin, and D-dimer are more elevated in MIS-C patients than KD. Lymphocyte counts and platelet counts are lower in MIS-C patients compared to KD. Cardiac manifestation of MIS-C include ventricular dysfunction, myocarditis, and/or coronary artery dilation/aneurysms [15•, 16, 35•, 36•, 37, 38, 39]. There have also been similarities of MIS-C to the myocarditis-like syndrome in adults with hyperinflammation that occurs weeks after the acute CVOID-19 infection [40].

Table 1. Diagnostic criterion for MIS-C and Kawasaki disease

	CDC MIS-C	WHO MIS-C	Complete KD	Incomplete KD
Age	<21 years	0–19 years	Usually 2–5 years of age	< 18 years
Fever	≥38.0°C for ≥24 h or subjective fever	Fever ≥3 days	Fever ≥5 days	Fever ≥5 days or infants with fever ≥7 days
	AND	AND		AND
Evidence of inflammation	≥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	More than one marker of inflammation: elevated CRP or ESR AND 3 or more of the following: anemia and thrombocytosis after the 7th day of fever, hypoalbuminemia, leukocytosis, transaminitis, sterile pyuria
	AND	AND	AND	
Multisystem involvement	≥2 organ systems involved: cardiac, renal, pulmonary, hematologic, gastrointestinal, dermatologic, or neurologic	≥2 of the following: mucocutaneous inflammation (rash, bilateral, non-purulent 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, non-purulent conjunctivitis; edema and redness of the hands and feet; and/or cervical lymphadenopathy of ≥1.5 cm	
Cardiac abnormalities indicative of involvement	Abnormal biomarkers: elevated troponin and/or BNP or NT-pro-BNP ECG	Same as CDC MIS-C	Cardiac involvement defined as *Z* score of LAD or RCA ≥2.5; coronary artery aneurysm;	Same as complete KD; abnormal echocardiogram is diagnostic of incomplete KD

Table 1. (Continued)

	CDC MIS-C	WHO MIS-C	Complete KD	Incomplete KD
	changes: conduction block, ST segment elevation, myocardial ischemia, low voltage) Echocardiographic findings: *Z* score of ≥2 in any of the proximal coronary arteries Ventricular dysfunction (right, left, or both), Mitral regurgitation, pericardial effusion		or ≥3 features of decreased LV function, mitral regurgitation, pericardial effusion, or LAD or RCA *Z* scores 2–2.5	even in the absence of multiple laboratory findings
	AND	AND	AND	AND
Additional required features	Positive for SARS-CoV-2 infection by RT-PCR, serology, or antigen test or exposure within 4 weeks 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 etiology or diagnosis	No alternative etiology or diagnosis
	AND	AND		
	No alternative etiology or diagnosis	No alternative etiology or diagnosis		

BNP brain natriuretic peptide, *CDC* center for disease control, *CRP* c-reactive protein, *ECG* electrocardiogram, *ESR* erythrocyte sedimentation rate, *IL-6* interleukin 6, *KD* Kawasaki disease, *LAD* left anterior descending artery, *LDH* lactate dehydrogenase, *LV* left ventricle, *MIS-C* multisystem inflammatory syndrome in children, *NT-pro-BNP* N-terminal pro-hormone brain natriuretic peptide, *PT* prothrombin time, *PTT* partial thromboplastin time, *RCA* right coronary artery, *WHO* World Health Organization

Treatment

MIS-C treatment

There are notable differences between the threshold for treatment in children with MIS-C and KD. In MIS-C, the diagnostic criterion of fever is defined by the Centers for Disease Control as ≥38.0 °C for ≥24 h, whereas the diagnostic

criterion of fever in KD is defined by at least 5 days of high fever (usually ≥38.5–40 °C) [41]. Both require other signs and symptoms of inflammation, vasculitis, and the absence of other etiologies to explain the illness. The different laboratory features between MIS-C and KD are described above. In both KD and MIS-C, the first-line treatment is intravenous immunoglobulin (IVIG) [14–16, 35•, 36•, 38, 42–44]. In all reviews and case series of reported MIS-C, 70–80% of patients received IVIG, and the majority improved and had recovery of cardiac function [15•, 16, 35•, 36•, 38, 42–44]. Patients presenting with poor ventricular function may need to have IVIG in divided doses in order to tolerate the fluid load [15•]. Additionally, children who present in vasodilatory or distributive shock often receive multiple fluid boluses and require diuresis after stabilization to treat the ensuant volume overload. In a recent review of 953 MIS-C patients, inotropic support maybe needed in up to 73.3% of patient with hypotension or ventricular dysfunction [45••].

Children with MIS-C can develop coronary artery dilation, similar to KD, and may require adjunctive therapies such as infliximab, glucocorticoids, or anakinra [41, 44, 46, 47]. Treatment has been given in MIS-C for coronary involvement with a *Z* score of ≥2 in any of the proximal coronary arteries. This treatment threshold is slightly lower than the standard KD guidelines wherein adjunctive treatment is generally indicated with a coronary artery *Z* score ≥2.5 [41]. Like KD, MIS-C is considered to be refractory to IVIG if fever persists ≥36 h after completion of the immunoglobulin infusion or if there is progression of the coronary artery dilation. In these cases, infliximab has become an important adjunct in the treatment of MIS-C. Abdel-Haq et al reported that 92% (12/13) of their MIS-C patients required infliximab treatment after these children failed IVIG [48]. Glucocorticoids can be considered for patients with macrophage activation syndrome or cytokine release syndrome [44]. In a systemic review of 783 cases of MIS-C, 44% of the patients received intravenous steroids [49••]. A recent retrospective study by Ouldali et al. demonstrated that treatment with combined IVIG and methylprednisolone versus IVIG alone was associated with more favorable fever course [50•]. Anakinra is an alternative to glucocorticoids if the patient is refractory to glucocorticoids [44].

Children with MIS-C are prone to hypercoagulation and may have an indication for anti-thrombotic therapy. Those with coronary artery aneurysms are at increased risk for myocardial infarctions. MIS-C patients who meet criteria for complete or incomplete KD should receive low-dose antiplatelet therapy and anticoagulation depending on the degree of coronary artery dilation [41]. Systemic anticoagulation may be considered in MIS-C patients with poor LV function [15•, 44]. In children at risk for venous thromboembolism or pulmonary embolus due to hypercoagulability, the initiation of therapy to prevent thromboembolism may be considered [44]. In all situations, the risk for bleeding versus clotting must be carefully weighed throughout the acute presentation when thrombocytopenia is present in varying degrees.

Prognosis

The prognosis of COVID-19 infection is good in general pediatric patients. However, children with congenital heart disease and poor ventricular function

are at higher risk for severe disease than the general pediatric population [51, 52]. This is similar to reports in adults with acute COVID-19 where underlying cardiovascular disease is associated with worse outcome [53•, 54]. In the case of MIS-C, it is unclear if children with heart disease or a predisposition for heart disease (i.e., those with an underlying genetic abnormality that increases their risk for cardiomyopathy) are at greater risk for cardiac involvement. Despite severe illness in MIS-C population, the mortality is reported to be around 1.5–1.9% [45••, 49••].

An important area of concern is the risk of sports participation after MIS-C. Acute myocarditis involvement in MIS-C patients should include exercise restriction for 3 to 6 months similar to other viral myocarditis [55]. Children with MIS-C should have an electrocardiogram and an echocardiogram at diagnosis and cardiology follow-up after hospital discharge before any recommendations about sports participation can be made. Exercise stress testing may be helpful in documenting the safety of return to play after MIS-C.

Future

COVID-19 infection is an evolving disease, and information changes as we learn more about the acute and chronic cardiac effects in children. There is more to learn about the cardiac involvement seen in acute illness and in MIS-C. It has yet to be determined if children with underlying heart disease or a predisposition for cardiac disease are at greater risk for cardiac sequelae. This includes children with congenital heart disease, cardiomyopathy, and those with a genetic risk for cardiomyopathy. Moreover, new SARS-CoV-2 variants may evoke different immune responses that impact the development and manifestations of MIS-C. Certainly, understanding the mechanism of MIS-C and the therapeutic interventions with the greatest benefit and lowest side effect profile will take multi-center collaborations and basic research focused on the immune response to SARS-CoV-2. The current goal of vaccine development and administration is to reduce morbidity and mortality from the virus, but studies are needed for each vaccine to determine the efficacy of preventing infection altogether, the duration of protection, and the immune response to repeated vaccinations. Future research is needed to study the long-term outcomes of children after acute COVID-19 and MIS-C.

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