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Review

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Cardiovascular involvement in multisystem inflammatory syndrome in children with COVID-19

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Abstract

In children, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections typically result in a less severe coronavirus 19 (COVID-19) presentation than in adults. However, a subset of children presents with severe multisystem inflammation associated with recent SARS-CoV-2 infection or COVID-19 exposure in the previous weeks. The Center for Disease Control (CDC) has termed this condition a multisystem inflammatory syndrome in children (MIS-C). MIS-C causes significant cardiovascular involvement, which can be a determinant of clinical course and outcomes. A subset of MIS-C patients presents with hypotension and shock either from acute myocardial dysfunction or systemic vasodilation, with at least of third of patients developing cardiac manifestations from the illness. In addition, myocarditis, pericarditis, valvular regurgitation, coronary artery involvement, and arrhythmias have been reported, with a smaller subset of patients requiring extracorporeal membrane oxygenation. Here, we report our institutional experience of MIS-C over the last year and present a narrative review of cases reported in the literature. In addition, we discuss the clinical protocol of diagnosis and acute and follow-up management of these patients with MIS-C.

Keywords: MIS-C, COVID-19, cardiac function, coronary artery dilation

INTRODUCTION

The 2019 coronavirus (COVID-19) pandemic has led to significant morbidity and mortality throughout the world. During the initial phases of the COVID-19 pandemic, it was believed that children were not susceptible to the severe illness that was primarily seen in adults; however, in April of 2020, there were reports of Kawasaki like illness related to COVID-19 in children associated with significant multi-organ dysfunction[1-3]. This constellation of symptoms was named multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 by the Centers for Disease Control (CDC) and other public organizations[4]. The CDC case definition of MIS-C includes the presence of fever, laboratory evidence of inflammation, and multisystem organ involvement without alternative plausible diagnoses, as well as evidence of COVID-19 infection or recent exposure to a COVID-19 case. In addition to the presentation with persistent fever, asthenia, prominent gastrointestinal symptoms, and Kawasaki like disease, patients with MIS-C have manifested widespread cardiovascular involvement, including cardiac dysfunction, coronary artery dilation, myocarditis, myocardial stunning, and shock, with a majority of them requiring intensive care therapy due to hemodynamic instability[5,6].

While the vast majority of patients recover from their illness, it is estimated that 6%-14% continue to have myocardial dysfunction at discharge from their hospitalization, highlighting the need to closely follow these patients as an outpatient to monitor for long-term sequelae[6].

In this article, we present the cardiovascular involvement in MIS-C, review the acute management and discuss the cardiac outcomes of this illness as known to date.

METHODOLOGY FOR LITERATURE SEARCH

Each author reviewed available literature on MIS-C published between April 1, 2020, and June 30, 2021. Papers were obtained by searching through PubMed and Google Scholar, focusing on manuscripts discussing cardiovascular involvement with MIS-C and treatment. Particular emphasis was placed on identifying multi-center studies given that the number of MIS-C patients at individual centers is low; however, when applicable and related to the section, single-center studies were included. For each section, the authors selected the papers they felt were most relevant to the subheading and shared them with the rest of the authors for approval and discussion. There were no significant disagreements among the authors in the selection of pertinent literature.

CARDIO-VASCULAR INVOLVEMENT IN MIS-C

Acute cardiovascular presentation

The clinical onset of MIS-C typically occurs at 2-6 weeks after the initial COVID-19 infection. Cardiovascular involvement is common and can range from mild ventricular dysfunction to severe refractory cardiogenic, vasodilatory shock, or significant arrhythmia[6].

The predominant initial presenting symptoms include fever and malaise, with is usually present in all patients[7-9]. Gastrointestinal manifestations, including abdominal pain, nausea, and vomiting, are also present in most cases, with one case series of 70 patients noting up to 84% with these symptoms[7-9]. In addition, some patients have been noted to have Kawasaki-like features, which include rash, conjunctivitis, and peeling of the skin; compared to their counterparts with Kawasaki, patients with MIS-C tended to be older, have lower platelet counts, and a higher prevalence of cardiovascular involvement[10,11].

Table 1 highlights some of the clinical features from our institution's patient cohort[7].

Many patients with MIS-C have significant hypotension secondary to cardiogenic or vasodilatory shock, requiring additional supportive measures in up to 77% of patients[8,9]. In addition, cardiac dysfunction, including a myocarditis-like picture, can be present in third or more cases, with other centers reporting significantly higher prevalence[6,12,13].

We have previously described our experience with 54 patients diagnosed with MIS-C, with a median age of 6.8 ± 4.4 years[7]. Similar to other studies, cardiovascular involvement was prevalent in our cohort. Significant hypotension due to depressed left ventricular (LV) systolic function, persistent tachycardia, and signs of low cardiac output were present on admission or developed early during the admission in 52% of patients in our cohort. Moreover, fulminant heart failure developed in four patients, requiring veno-arterial extracorporeal membrane oxygenation (ECMO) support[7].

Compared to COVID-19 infection, MIS-C tends to lead to more significant acute hemodynamic manifestations. A recent report from Feldstein *et al.*[12] reviewed 1314 hospitalized children and adolescents younger than 21 years of age with COVID-19-related illness from 66 hospitals in 31 states and compared clinical presenting characteristics of patients with MIS-C to those with acute COVID-19 infection. In their cohort, patients with MIS-C were more likely to have cardiorespiratory involvement (56.0% *vs.* 8.8%; 95%CI: 42.4%-52.0%), cardiovascular without respiratory involvement (10.6% *vs.* 2.9%; 95%CI: 4.7%-10.6%), and mucocutaneous symptoms without cardiorespiratory involvement (7.1% *vs.* 2.3%; 95%CI: 2.3%-7.3%)[12].

In summary, the acute clinical presentation is variable with overlapping signs and symptoms. Unfortunately, many patients present with significant hemodynamic instability requiring critical care at presentation or short after initial admission.

Myocardial dysfunction

LV dysfunction, with a left ventricular ejection fraction (LVEF) less than 55%, is relatively common among patients presenting with MIS-C, with the majority of patients having some degree of cardiac dysfunction[13]. In New York City, Kaushik *et al.*[14] reported 33 patients with MIS-C and noted that greater than 50% developed LVEF less than 50% in their cohort. The degree of myocardial involvement can be quite significant, requiring significant inotropic and circulatory support. Our center saw at least 2 cases of myocardial stunning, with both patients requiring ECMO support [Supplementary Video 1]. Belhadjer *et al.*[15] reviewed 35 patients presenting with acute cardiogenic shock secondary to MIS-C; they reported that 28% of their patients had significantly reduced LVEF < 30%, with another 28% requiring ECMO support due to poor clinical condition. Their study focused on only patients with LV systolic dysfunction, so their reported percentage of patients with severely reduced LV function is higher than other studies.

Recent studies have looked at sensitive markers of LV dysfunction, and particularly global left ventricular longitudinal strain in relation to patients with MIS-C. For example, in a study of 28 patients with MIS-C, compared to patients with Kawasaki disease and those with structurally normal hearts, patients with MIS-C had reduced global left ventricular longitudinal strain and left atrial strain[16]; another study of 25 patients through Boston Children's Hospital found similar results[17].

Interestingly, while they noted that 80% of patients with initially decreased LVEF normalized prior to discharge, 36% of the patients continued to have abnormal strain at 8 days post discharge[17].

Table 1. Clinical characteristics of our cohort of patients

Parameter	Value
Age, years	6.8 ± 4.4
Fever, *n* (%)	53 (98.0)
Rash, *n* (%)	26 (48.0)
Lymphadenopathy, *n* (%)	13 (24.0)
Gastrointestinal symptoms, *n* (%)	40 (74.0)
Respiratory distress, *n* (%)	15 (28.0)
Hypotension, *n* (%)	28 (52.0)

Similarly, our group noted that 42% had abnormal LVEF < 55% at presentation; however, almost 2/3 had abnormal global left ventricular longitudinal strain[7]. At a median of 10 weeks follow up, only one patient of 54 initial studied had an abnormal LVEF < 55% while 6 of 54 had abnormal global left ventricular longitudinal strain, highlighting that the acute inflammation may have led to subclinical residual myocardial damage[7].

Valvular regurgitation and pericarditis

Valvular regurgitation [Figure 1] has been noted in up to 40% of patients with pericardial effusions seen in slightly more than 25%[13,18]. However, severe valvular regurgitation and large pericardial effusions are rare[7,13]. Pericardial effusion [Figure 2] was typically noted at presentation or in follow-up echocardiography prior to discharge[7]. It was most commonly a small effusion that did not require intervention. There have been case reports of more significant pericardial involvement requiring pericardial drainage and ultimately surgical pericardial exploration and pericardiectomy, but these cases are rare[19]. Pericardial effusions seen at discharge were resolved approximately 8-10 weeks from the presentation[7]. None of our patients that initially had mitral regurgitation had residual mitral regurgitation at their 3 weeks follow-up[7].

Coronary artery involvement

Initial reports describing MIS-C indicated the presence of coronary artery abnormalities (dilation and aneurysm formation) in some of the affected patients [Figure 3]. The presence of fever, cutaneous changes, and conjunctivitis raised concerns for Kawasaki disease-like syndrome[20,21]. A systematic review of cases reported from multiple countries indicated that coronary artery abnormalities are present in about 20% of children affected with MIS-C[21,22]. A large study in the United States involving data collection from 66 hospitals in 31 states showed that coronary artery aneurysms (coronary artery Z score > 2.5) were present in 13.4% of patients. Most of the patients (93%) had mild aneurysms that regressed to normal size in 79.1% of the patients by 30 days[12].

Cardiac dysrhythmias

The development of conduction system abnormalities in MIS-C has been well documented and is a prominent cardiac finding. Studies report rates of 12%-67% of various electrocardiographic abnormalities ranging from first-degree atrioventricular (AV) block to sustained tachyarrhythmia[22,23]. First-degree AV block is frequently reported in patients with MIS-C with a prevalence of 19% to 25%[24]. A series of 32 patients showed a median onset of the first-degree block at 8 days from the start of symptoms and resolution at about three days after it appeared[25]. Most reported cases do not progress to an advanced grade AV block, although there are rare reports of high-grade heart block as a complication of MIS-C, with some requiring transvenous pacing[26].

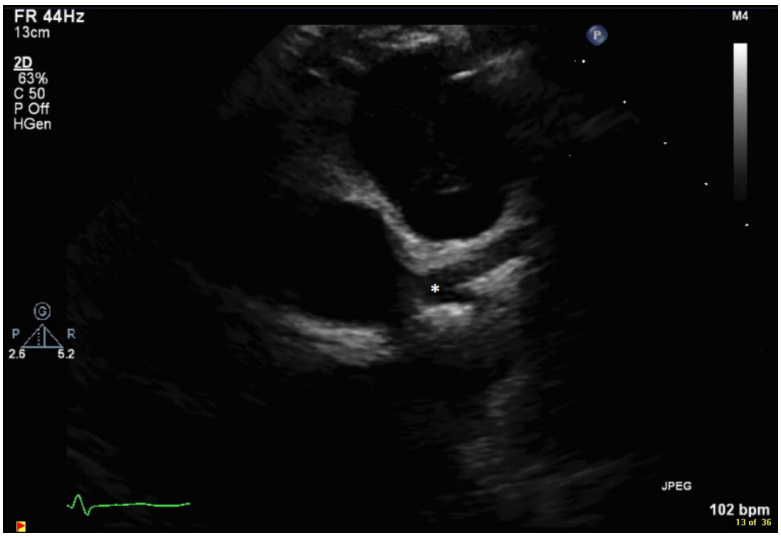

Figure 1. Left main coronary dilation in a patient with multisystem inflammatory syndrome in children. *Dilated left main coronary artery.

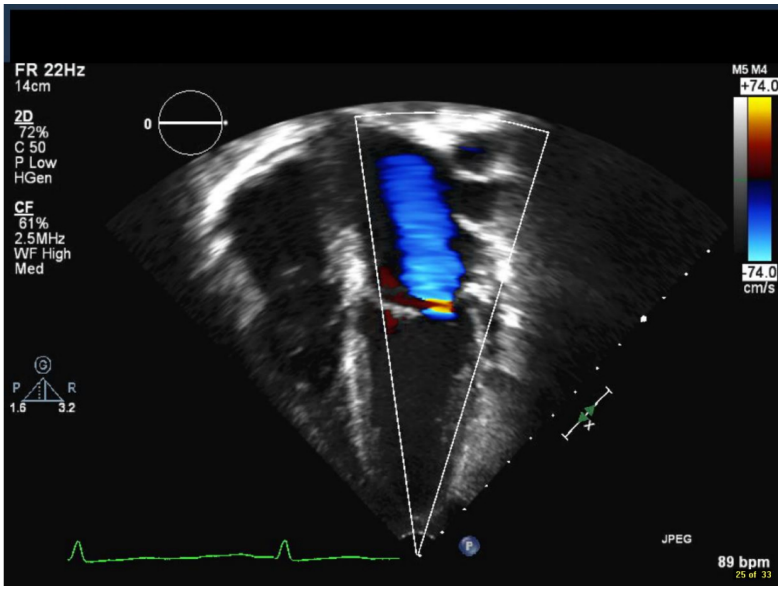

Figure 2. Moderate mitral regurgitation in a patient with multisystem inflammatory syndrome in children.

A large cohort of 63 patients described low amplitude QRS and transient T-wave inversion as the most common electrocardiographic abnormality[25]. Transient QTc prolongation was seen in 22% of patients[25]. Only 2/63 patients had atrial arrhythmias, with 11/63 experiencing a bradyarrhythmia[25]. ST-segment changes were rarely seen, affecting 5/63[25]. Figures 4 and 5 show the various electrocardiogram (EKG) manifestations of two of our patients who required ECMO support.

In the setting of myocardial inflammation, as is seen in MIS-C, electrocardiographic changes are expected. While most patients appear to have non-specific and transient changes on electrocardiogram, providers must be prepared that some will present with significant arrhythmia contributing to circulatory collapse and/or exacerbating cardiogenic shock.

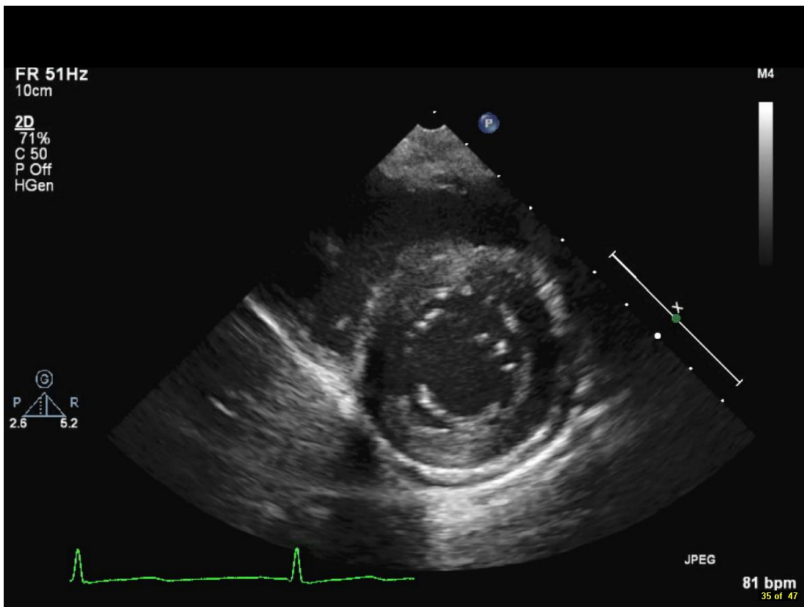

Figure 3. Small pericardial effusion in a patient with multisystem inflammatory syndrome in children.

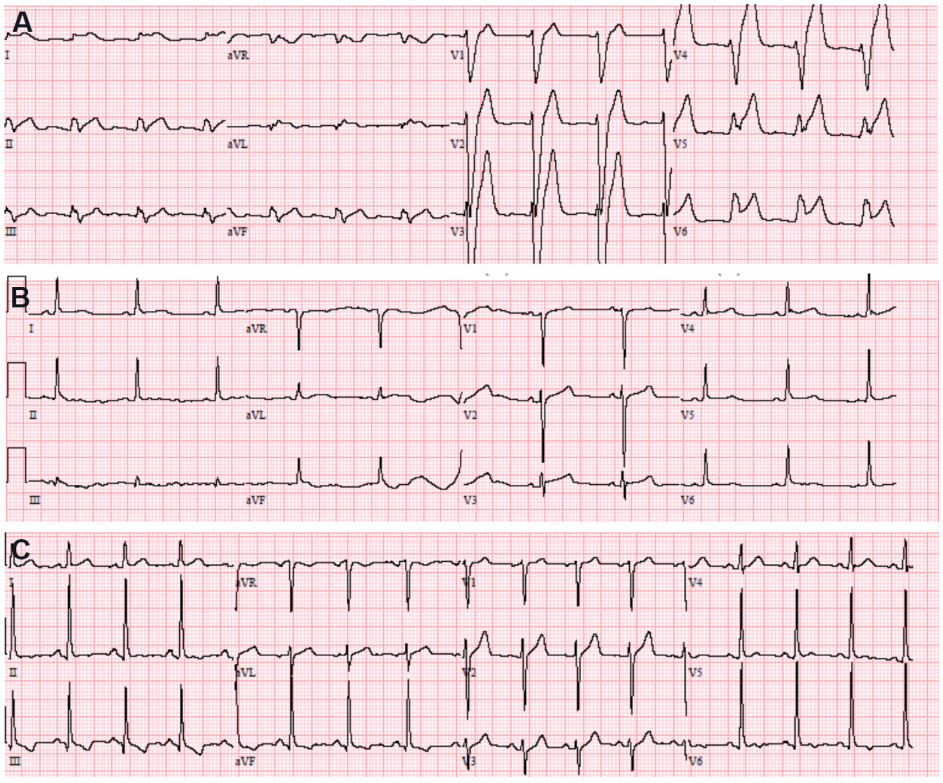

Figure 4. Longitudinal electrocardiogram findings for the patient with multisystem inflammatory syndrome in children who required ECMO support. (A) First degree AV block and significant ST-segment elevation on admission. (B) Flat T waves at 2 weeks follow up. (C) Persistent negative T waves in the inferolateral leads at 6 weeks follow up.

ACUTE MANAGEMENT OF MIS-C

Early recognition of MIS-C is essential to avoid worsening cardiovascular complications. In New York, the

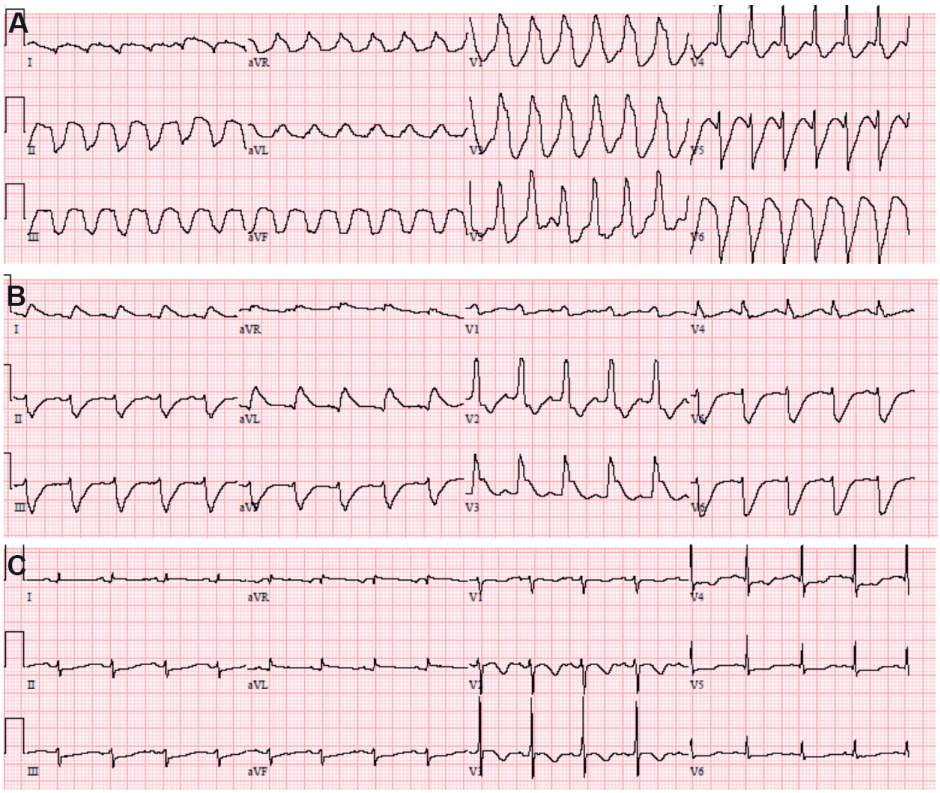

Figure 5. Electrocardiogram findings for another patient with multisystem inflammatory syndrome in children who required ECMO support. (A) Day 1 - ventricular tachycardia. (B) Day 2 - normal sinus rhythm with wide complex QRS. (C) Day 5 - normal sinus rhythm with non-specific T wave abnormalities.

implementation of a protocol for the identification and treatment of MIS-C led to early initiation of therapy for these patients[27]. Similarly, at our institution, we have evolved the protocol for evaluating and managing patients with MIS-C to intervene early in the clinical course and closely monitor the patient.

MIS-C cardiac protocol

In the emergency department

1. EKG;
2. High sensitivity troponin I;
3. Obtain an echocardiogram in the Emergency Department if:

a. Hemodynamically unstable, signs of shock, poor perfusion, lactic acidosis;
b. High sensitivity troponin I level > 50 ng/mL;
c. ECG shows arrhythmia or changes related to myocardial ischemia.

For MIS-C/Kawasaki-like presentation: upon admission to the floor/intensive care unit

1. EKG:

a. Baseline: upon admission (if not done in the emergency department);
b. Repeat minimum q3 days;
c. Repeat earlier:

i. Increase in troponin from baseline;
ii. Advancing therapies/persistent fever/rising inflammatory markers after intravenous immunoglobulin (IVIG);

iii. New need for inotropic support;
iv. New rhythm changes;
v. New physical examination findings (i.e., murmur, gallop, jugular venous distension, hepatomegaly);
2. High sensitivity troponin I level:
a. Baseline: upon admission (if not done in the emergency department);
b. Repeat daily while febrile;
c. Continue daily until down-trending × 2 days.
3. Echocardiogram:
a. Baseline: upon admission to the floor (if not obtained in the emergency department);
b. Repeat echocardiogram during hospital stay if:
i. Increase in troponin from baseline;
ii. Advancing therapies/persistent fever/rising inflammatory markers after IVIG;
iii. New need for inotropic support;
iv. New rhythm or EKG (ST/T wave) changes;
v. New physical examination findings (i.e., murmur, jugular venous distension, hepatomegaly, gallop).
c. Repeat prior to discharge if the previous echocardiogram was abnormal.

Post-discharge cardiology follow-up for MIS-C patients

General cardiac recommendations

1. Continue low dose aspirin till discontinued by Infectious Disease/Cardiology;
2. Avoid strenuous exercise/ competitive sports for 6 months or until permitted by Cardiology;
3. Call if there is any recurrence of fever or other symptoms.

Cardiology follow-up visits

1. First follow-up: 2 weeks after discharge from the hospital;
2. Second visit: 6-8 weeks from the discharge;
3. Then cardiology follow-ups at 6 months and one year from discharge (additional visits to be scheduled depending on the clinical course at follow-up);
4. Cardiac MRI to be done 6-12 months after diagnosis in patients who required intensive care admission.

TREATMENT PROTOCOL

During the early phases of the pandemic, given the overlap of MIS-C symptoms with Kawasaki disease, therapeutics consisted of IVIG and other immunomodulatory medications. In a survey of the International Kawasaki Disease Registry, 53% of participating sites reported using IVIG for all patients regardless of illness severity or symptoms; 64% of sites used steroids for critically ill patients[28]. Other immunomodulatory medications, including infliximab, tocilizumab, and anakinra, were used as well in patients with refractory MIS-C[28].

In our institution, patients who have confirmed diagnosis of MIS-C received first-line therapy with IVIG (2 g/kg IV infusion over 12-24 h) and aspirin (moderate dose 30-50 mg/kg divided q6H PO till afebrile for 2-3 days, then low dose aspirin 3-5 mg/kg to a maximum of 81 mg daily for 6-8 weeks). Patients who are refractory to IVIG therapy (persistent fever 24-36 h after completion of IVIG infusion) or patients who presented with severe hemodynamic instability received an additional (second-line) treatment with Infliximab or Solumedrol. Infliximab (10 mg/kg) was used more commonly as a second-line choice during the first wave of COVID19 and MIS-C, resulting in favorable outcomes[29]. Currently, Solumedrol, Infliximab and/or second IVIG infusion are considered second-line therapy at our center.

The most effective treatment for MIS-C continues to be debated. A recent multi-center study showed that IVIG and glucocorticoid therapy for patients with MIS-C compared to IVIG by itself is potentially correlated with a lower likelihood for systolic myocardial dysfunction[30]; however, an international cohort study has suggested no differences in short term outcomes when comparing IVIG plus steroids to IVIG or steroids by themselves[31].

CARDIAC OUTCOMES

Given the recent appearance of an MIS-C as a clinical entity, the illness's long-term cardiac outcomes on patients are unclear; however, recent studies have evaluated the short-term outcomes of these patients. Valvular regurgitation, pericarditis, and dysrhythmias appear to resolve within 10 weeks after initial diagnosis[7]. Additionally, left ventricular ejection fraction appears to normalize in most patients by 10 weeks follow up; however, 25% of patients had persistently reduced left ventricular global longitudinal strain at 10 weeks follow up[7]. A more recent study of 46 patients from the UK noted 44 patients with normal echocardiograms at 6 months follow up, with two patients having coronary enlargement that was persistent on follow up[32]. All patients had normal left ventricular systolic function[32].

At this time, it is unclear what the risk factors for cardiac dysfunction in MIS-C are. However, our group's research suggests that patients with persistently low left ventricular strain at their initial presentation echocardiogram are at risk for persistent cardiac dysfunction at 10 weeks follow up[7]. The National Institutes of Health has recently allocated funding for a prospective study looking at patients with MIS-C, deemed the "Long-Term Outcomes after the Multisystem Inflammatory Syndrome in Children" Trial, or MUSIC, to follow patients over 5 years. The study is currently recruiting participants across different centers in the United States.

CONCLUSION

In conclusion, MIS-C can lead to significant morbidity and mortality and is associated with multiple cardiovascular manifestations. However, prompt identification and management of these patients can lead to satisfactory outcomes for these patients. At this time, the long-term cardiovascular risk factors for these patients are uncertain, but it appears that most patients are asymptomatic at least 10 weeks follow up.

DECLARATIONS

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Authors' contribution

Performed reference collection and wrote the manuscript: Misra A, Safa R, Sanil Y, Blake JM, Charaf Eddine A, Balakrishnan P, Garcia RU
Re-edited the manuscript: Aggarwal S, Singh G

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

The authors consent to publication of our manuscript.

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