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DOI: 10.1542/peds.2021-050973

Journal: Pediatrics

Article Type: Regular Article


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Six Month Follow-up of Patients With Multisystem Inflammatory Syndrome in Children

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Conflict of Interest Disclosures: The authors have no conflicts of interest relevant to this article to disclose.

Funding/Support: The author(s) received no financial support for the research, authorship and/or publication of this article.
Abbreviations:
MIS-C: Multisystem inflammatory syndrome in children (MIS-C)
COVID-19: Coronavirus Disease 2019
KD: Kawasaki Disease
LV: Left Ventricle
LVEF: Left Ventricular Ejection Fraction
NYHA: New York Heart Association
IVIg: Intravenous Immunoglobulin
CMRI: Cardiac Magnetic Resonance Imaging

Article Summary:
This longitudinal cohort study of 50 children with MIS-C treated with immunomodulators in the acute phase reveals an uncomplicated and favorable 6 month cardiovascular prognosis.

What is known on this subject:
Myocardial dysfunction and coronary abnormalities are prominent early features of acute multisystem inflammatory syndrome in children (MIS-C). Persistent coronary aneurysm and/or low-normal or mild LV dysfunction has been reported after hospitalization.

What this study adds:
Early and mid-term prognosis after hospitalization and immunomodulation treatment for MIS-C is excellent with return to functional baseline, normalized LV systolic function, and resolved coronary abnormalities. However, persistence of diastolic dysfunction in a few patients confounds our understanding of MIS-C.

Contributors' Statement Page:
Drs Capone, Misra, Epstein, Romano, Rajan, Acharya, Hayes and Mitchell conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Drs Ganigara and Ms Kearney designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Drs Friedman, Blaufox, Cooper and Schleien conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Abstract

Background and Objectives:
Myocardial dysfunction and coronary abnormalities are prominent features of multisystem inflammatory syndrome in children (MIS-C). This study aims to evaluate the early and mid-term outcomes of MIS-C.

Methods:
This is a longitudinal 6-month cohort study of all children admitted and treated for MIS-C from April 17- June 20, 2020. Patients were followed about 2-weeks, 8-weeks and 6-months post-admission, with those with coronary aneurysms evaluated more frequently.

Results:
Acute, 31 (62%) patients required intensive care with vasoactive support, 26 (52%) had left ventricular (LV) systolic dysfunction, 16 (32%) had LV diastolic dysfunction, 8 (16%) had coronary aneurysms (Z-score >/=2.5), and 4 (8%) had coronary dilation (Z-score <2.5). 48 patients (96%) received immunomodulatory treatment. At 2-weeks, there was persistent mild LV systolic dysfunction in one patient, coronary aneurysms in two, and dilated coronary artery in one. By 8-weeks through 6-months, all patients returned to functional baseline with normal LV systolic function and resolution of coronary abnormalities. CMRI performed during recovery in select patients revealed no myocardial edema or fibrosis. Some patients demonstrated persistent diastolic dysfunction at 2-weeks (5, 11%), 8-weeks (4, 9%) and 6-months (1, 4%).

Conclusion:
Children with MIS-C treated with immunomodulators have favorable early outcomes with no mortality, normalization of LV systolic function, recovery of coronary abnormalities, and no inflammation or scarring on CMRI. Persistence of diastolic dysfunction is of uncertain significance and indicates need for larger studies to improve understanding of MIS-C. These findings may help guide clinical management, outpatient monitoring, and considerations for sports clearance.
Introduction:

Multisystem inflammatory syndrome in children (MIS-C) is a new post-infectious inflammatory disorder that has emerged during the COVID-19 pandemic. Critical illness is a prominent feature, with up to 80% of patients requiring intensive care, approximately 50% showing features of LV systolic dysfunction and myocarditis, and 10-20% developing coronary artery aneurysms (Z-score ≥ 2.5). 1-4 For patients presenting with preserved systolic function, myocardial injury may still occur, detected by echocardiographic measures of diastolic dysfunction. Although MIS-C has many similarities to other inflammatory syndromes such as Kawasaki disease (KD), children with MIS-C tend to be older and have more intense inflammation and myocardial injury than children with KD.3 Coronary artery involvement is the major cardiovascular sequelae of KD and coronary dilation associated with KD tends to regress within 2 years.5,6 However, the long-term complications of MIS-C are still unknown. This study describes the management and early to mid-term outcomes of a cohort of pediatric patients 6 months after admission for MIS-C.

Methods:

This is a 6-month follow-up study of pediatric patients (< 21 years of age) hospitalized for MIS-C between April 17, 2020 and June 20, 2020 at Cohen Children’s Medical Center. This study was approved by the Northwell Health Institutional Review Board with informed consent waived. The clinical presentation and hospitalization of some patients (n=31) included in this report have been published previously by Capone et al. and/or as part of a multicenter publication.2,4 This paper differs from the aforementioned papers as it adds more patients to the acute phase analysis and more importantly longitudinal data. Further, diastolic function was added to the analysis along with CMRI results. Patients were included if they met the CDC case definition for MIS-C and if
they had evidence of SARS-CoV-2 infection by either detection of serum antibodies or nucleic acid from a nasopharyngeal specimen (PCR+). 7,8

Patients received immunomodulatory treatment and anti-coagulation as per our institutional guideline (supplemental appendix). Patients were clinically followed at approximately 2 weeks, 8 weeks and 6 months post admission. Some patients were seen more frequently as clinically indicated.

Serial echocardiograms were performed at the time of admission and then as clinically indicated or per protocol. Ventricular function and coronary dimensions were tracked serially from date of admission to 6-month follow up. Boston Children’s Hospital Z-score system was utilized for all echocardiographic measurements. 9 Left ventricular (LV) systolic dysfunction was defined as a LV ejection fraction (LVEF) < 55% by 5/6 area-length method and graded as mild (LVEF 45-54%), moderate (LVEF 35-44%), or severe (LVEF < 35%) as previously described. 4 A patient was considered to have diastolic dysfunction (yes/no) if at least 2 parameters (E/A, e’, or E/e’) were abnormal. The mitral inflow E/A Doppler profile was considered abnormal if the E and A waves were fused, or if the E/A ratio had a Boston Children’s Hospital Z-score > 2.0. The e’ velocity and E/e’ ratio, either septal or lateral, were considered abnormal if either had a Boston Children’s Hospital Z-score > 2.0. Aneurysm and dilation of a proximal coronary artery (right coronary artery, left main coronary artery, and/or left anterior descending coronary artery) were defined using Z-scores as per latest AHA Kawasaki guidelines (dilation 2.0-2.49, small aneurysm ≥2.5 to <5, medium aneurysm ≥5 to < 10, and large aneurysm ≥10). 5 Qualitative lack of tapering was used to describe an abnormal coronary appearance that did not meet criteria for dilation or aneurysm.
Cardiac MRI (CMRI) was performed 2-4 weeks after discharge from hospital as per our institutional protocol in follow up of clinically diagnosed myocarditis such as patients with LV systolic dysfunction, elevated troponin, and/or EKG changes. All CMRI studies were performed without general anesthesia or sedation. Image analysis was done using Circle software (CMRI-42).

Continuous variables are summarized as mean and standard deviation or median and interquartile range (IQR) as appropriate. Categorical variables are presented as frequency. All analyses were performed using Excel (Office Professional +13, Microsoft, Redmond, Washington).

Interrater reliability was assessed using Cohen’s Kappa coefficient. Multiple statistical classifications describing degree of reliability are reported in the literature. A commonly used methodology by Landis et al categorizes agreement as follows: < 0.01, poor agreement; 0.01 - 0.20, slight agreement; 0.21 - 0.40, fair agreement; 0.41 - 0.60, moderate agreement; 0.61 - 0.80, substantial agreement; 0.81 - 1.00, almost perfect agreement. Since interrater reliability demonstrated substantial agreement for LVEF and substantial agreement for coronary abnormalities (including lack of tapering), the data on the formal TTE report was used for analysis.

Results:

Acute Presentation

Fifty consecutive patients met CDC criteria for MIS-C and had laboratory evidence of SARS-CoV-2 infection during this study period. Our cohort was predominantly male (56%) with a median age of 8.5 years (range 9 months to 17 years). The epidemiologic characteristics and
clinical profile of patients were similar to our previously reported data\textsuperscript{4} (Table 1). Notably, CRP was markedly elevated (median 204 mg/L; IQR 122- 291; ref < 5) and the platelet count was low-normal (median 172 K/uL; IQR 122-232) in our cohort.

Cardiac abnormalities present on admission and followed in this study are detailed in Table 2. Thirty-three patients (66\%) had cardiovascular manifestations that included LV systolic dysfunction, LV diastolic dysfunction, or coronary dilation or aneurysm. Twenty-six patients (52\%) had LV systolic dysfunction and required an intensive level of care with vasoactive support. Of these 26 patients, 11 also had LV diastolic dysfunction and 10 had coronary dilation or aneurysms. Two patients had aneurysms only without any type of LV dysfunction. Five patients had diastolic dysfunction only without evidence of LV systolic dysfunction or coronary dilation/aneurysm. Of note 14 patients (28\%) showed an abnormal coronary appearance (lack of tapering) that we followed to assess for longitudinal significance, if any.

Plasma brain natriuretic peptide (pro-BNP) and plasma C-reactive protein (CRP) were more elevated in patients with LV systolic dysfunction than those without [BNP 9,874 pg/mL (IQR 4,514-24,152) vs 3151 pg/mL (IQR 1343-4424), p value = 0.005, and CRP 233 mg/L (IQR 142-289) vs 148 mg/L (IQR 95-212), p value= 0.03 respectively]. Neither were associated with the development of coronary abnormalities. Although plasma high-sensitivity troponin T levels were elevated in patients with LV systolic dysfunction compared to those with normal function [44 ng/L (IQR 20-110) vs 21 ng/L (IQR 6-79) p=0.14\)], this was not statistically significant. Additionally, troponin T level was not associated with the development of coronary abnormalities. Although peak levels of CRP, pro-BNP and troponin T were more elevated in patients with cardiac manifestations, we were not powered to assess sensitive lab cutoffs predictive of cardiac
abnormalities. When assessed as dichotomous variable, abnormalities in initial lab tests were no different between those with cardiac manifestations vs those without.

Most patients exhibited rapid clinical improvement, with 48 patients (96%) having received treatment as per our institutional guideline (Table 1). Thirty-five patients (70%) were discharged on tapering steroids, forty-six patients (92%) with Aspirin and 23 patients (46%) with Enoxaparin or Apixaban as per our institutional guidelines.

The median length of hospital stay for the entire cohort was 5 days (IQR 4-7). There were no in-hospital deaths, and no patient required ECMO support. Of the 26 patients with LV systolic dysfunction at admission, 18 patients (69%) had normalization of the LV systolic function by discharge; 4 patients (15%) had persistent but improved LV systolic dysfunction. The remaining 4 patients had mild dysfunction during admission and did not have a discharge echo to assess. Recovery of function occurred at a median of 3 days with an interquartile range of 1-8 days. Coronary findings were unchanged at discharge.

2-week follow-up

Of the 47 patients who presented for the 2-week follow up visit, 22 (47%) reported fatigue with ordinary activity. Of these 22 patients, 18 had features of shock and myocardial systolic dysfunction at initial admission. All other patients were asymptomatic.

Platelet levels were elevated at 2 weeks compared to presentation (median 463 K/uL (IQR 375-541) vs median 172 K/uL (IQR 122-232), p = <0.001). All other markers had normalized including
CRP (median 0.14 mg/L (IQR 0.1-0.7), troponin T (median 6 ng/L (IQR 6 -7)) and BNP (median 63 pg/mL (IQR 54-112)).

The LV systolic function was normal in all except one patient who had persistent mild LV systolic dysfunction (LVEF 54%). [Table 2 and Figure 1] Diastolic dysfunction was noted in 5 patients (11%), all of whom who had mild LV systolic dysfunction during hospitalization, 4 of whom also had troponin elevation. Of these 5 patients with diastolic dysfunction, 3 had the dysfunction in the acute phase. The coronary abnormalities were improving: two (4%) had coronary aneurysms, one (2%) had coronary dilation and 12 (21%) showed lack of tapering. No new coronary abnormalities were noted. [Table 2 and Figure 2]

All patients were tapered off steroids once inflammatory markers normalized (range 10-21 days) and continued on anti-coagulation with hematology follow-up as per institutional guidelines.

**8 -week follow-up**

Of the 42 patients who presented for the 6-8 week follow up visit, 5 (12%) continued to have fatigue with regular activity. All patients had normal LV systolic function and resolved coronary aneurysms and dilation. [Table 2, Figure 1 and 2] However diastolic dysfunction persisted in 4 patients (9%) and qualitative coronary abnormalities were noted in five (12%) patients. No new coronary abnormalities were noted.

Anticoagulation with Enoxaparin or Apixaban was discontinued in all patients prior to the 8-week visit after normalization of inflammatory markers and platelet count as per institutional guidelines. Aspirin was discontinued at the 8 week visit only upon normalization of the coronaries and platelet count.
Cardiac MRI (CMR) was performed in 11 patients with prior LV systolic dysfunction and troponin elevation during admission. There was no evidence of persistent edema or fibrosis in any patient. No coronary artery dilation or aneurysms were seen.

6-month follow-up

Of the 25 patients who presented to the 6-month follow up visit, all were asymptomatic and at their functional baseline. Echocardiography showed normal LV systolic function and normal coronary arteries. [Table 2, Figure 1 and 2] This was true for both patients who initially presented with cardiac abnormalities (12/25, 48%) and for those that presented with normal systolic function and coronary appearance (13/25, 52%). One patient, though asymptomatic, continued to demonstrate LV diastolic dysfunction. Of note this patient had LV dysfunction and troponin elevation during hospitalization however there was no inflammation or fibrosis on CMRI at 8 weeks. By the 6 month visit, 31/33 (94%) patients with initial cardiac abnormalities were seen in follow up over the time period of the study.

Discussion:

This study reports on the early and mid-term outcomes of 50 children recovering from MIS-C after hospitalization in the acute phase. The epidemiologic characteristics and clinical profile of the acute phase were similar to other single-center and multicenter studies. 1-3 Children experienced intense inflammation with most patients presenting with shock, cardiac dysfunction and/or coronary abnormalities. For patients with cardiovascular involvement, most LV systolic dysfunction resolved within 7-10 days and most coronary aneurysms resolved by 2 weeks. The rapidity of resolution in our study is unlike the typical course of viral myocarditis and Kawasaki
disease and suggests that cardiac manifestations are a result of systemic inflammation and vasodilation rather than immune infiltrate mediated damage to the myocardium.

Despite normalization of systolic function, some patients continued to have subjective symptoms of fatigue and exercise intolerance at the 2- and 8-week visit. These symptoms had resolved by 6 months in all patients. The persistent functional morbidity at 2 and 8 weeks after acute illness and normalization of LV function is likely related to a combination of acute severe inflammation, cytokine storm, and critical illness in the acute phase as well as post-viral infection fatigue and subtle subclinical neurological or cardiovascular post-COVID sequelae. 12,13

There are no comparative studies evaluating the treatment protocols of MIS-C to date. Our patients were uniformly treated as per our institutional guideline which shares similarities with expert consensus recommendations from the American College of Rheumatology and other institutional protocols. 14,15 This treatment protocol was associated with rapid clinical improvement and reduction in inflammatory markers in most patients, with no mortality and with improvement in cardiac findings. None of our patients had secondary infections, showed evidence of coronary thrombosis, developed a recognized clinical thrombotic event, or had a bleeding complication from steroids or anticoagulation. The clinical improvement noted here without adverse outcome is associated with a specific treatment strategy that may assist providers in caring for patients with MIS-C while we await further guidance from multicentered and comparative effectiveness studies.

The proportion of patients with coronary abnormalities at initial diagnosis was high (52%), due to our inclusion of qualitative coronary artery abnormalities such as lack of tapering in addition to dilated or aneurysmal coronary arteries. Loss of normal tapering of coronary artery is known to be associated with KD although the exact prognostic significance is unknown. 16 We included it here
as an abnormality to follow given reports of coronary aneurysms in the sub-acute and convalescent phase of MIS-C. Fortunately lack of tapering resolved by 6 months with no new development of coronary abnormalities noted at the 2 to 8 week follow up, when our follow up was highest and when expected coronary abnormalities would be seen.

While coronary artery dilation has been described in febrile non-KD patients, coronary aneurysms are not. In our cohort, 16% of patients presented with aneurysmal coronary arteries (Z score ≥ 2.5) in the acute phase. There was relative thrombocytopenia in the acute phase and thrombocytosis at 2 week follow up that resolved by 6 months. While this could suggest a vascular pathology similar to KD, 100% of these aneurysms regressed by 8 weeks. It is unclear if this regression is treatment-related, or the natural progression of the vasculitis noted in MIS-C. Until this is known, continuing anticoagulation in MIS-C particularly through the thrombocytosis phase noted on follow-up, may have important prognostic implications.

A large subset of our MIS-C cohort had LV systolic dysfunction and troponin elevation suggestive of myocyte injury. However, unlike viral myocarditis, most patients demonstrated rapid recovery. Though systolic function resolved, diastolic dysfunction, or impaired relaxation, persisted in a subset of patients. Diastolic dysfunction has been associated with impaired microvascular function and low grade inflammation in Kawasaki disease and may be suggestive of subclinical myocardial injury unable to be detected by LVEF, a global marker of cardiac function. The presence of diastolic dysfunction is consistent with other MISC studies however its clinical importance and long-term implication are currently unknown.

Due to the extensive myocardial involvement and elevation of biomarkers reported in MIS-C, recent return-to-sports guidance has suggested restricting children for 3-6 months post-
illness as in direct infiltrative viral myocarditis. A subset of patients with direct infiltrative myocarditis will develop fibrosis/myocardial scarring as detected by late gadolinium enhancement on MRI. This finding has been associated with long-term cardiovascular dysfunction and mortality. In MIS-C, CMRIs performed in acutely hospitalized patients have found mostly myocardial edema and have not yet reported on fibrosis in or after the convalescent phase. We performed cardiac MRIs during the convalescent phase in 11 patients with reduced LV function and elevated troponin. Fortunately for these children, there was no evidence of persistent edema or fibrosis indicating myocardial scarring. The rapid improvement of cardiac findings and lack of reported fibrosis in the convalescent phase may have implications for sports clearance and risk of arrhythmia after recovery from MIS-C. Perhaps children may not need to be exercise-restricted for as long as they would for direct infiltrative viral myocarditis though larger studies are needed to confirm this. Given our findings, our current practice is to allow sports participation in patients with normalization of their inflammatory markers and systolic cardiac function at 8 weeks after hospital discharge.

**Study Limitations:**

This is a single-center case series that has several limitations. First, the MIS-C case definition is broad. Consequently, some patients included in this study may have had a different underlying cause including acute COVID-19 with “cytokine storm” or classic KD rather than MIS-C, given the difficulty in differentiating these clinical diagnoses. Similarly, it is also possible that we underestimated the incidence of MIS-C in our patient population. As we included only cases with confirmed SARS-CoV-2 infection in our study, limited availability of molecular or serologic tests...
may have led to exclusion of children who met clinical criteria for MIS-C but did not have a positive SARS-CoV-2 test.

Second, this is a small single center cohort study. Although our patients with cardiac abnormalities noted during hospitalization improved, eight patients without acute echocardiographic abnormalities were lost to follow-up at 8 weeks. These patients may have developed coronary aneurysms or other cardiac sequela. More patients were lost to 6 month follow-up, though all those with functional deficits or qualitative coronary abnormalities returned and showed improvement. It is unlikely that we are missing new coronary aneurysms at 6 months in patients with normal coronary artery Z scores at 8 weeks.

While interrater reliability demonstrated substantial agreement for LVEF and substantial agreement for coronary abnormalities, we did not assess interrater reliability for diastolic dysfunction. Assessment of diastolic dysfunction in children has poor interobserver agreement making these measures unreliable and may adversely affect interpretation. However, until better diastolic criteria are universally available, given the findings of Matsubara et al20, it is important to assess diastolic dysfunction using all available parameters as this may be important to long term follow-up and patient care.

Finally, although our favorable outcomes were associated with our broad immunotherapy and anticoagulation, without a comparison group, small single-center cohort studies do not provide evidence for effective treatment of MIS-C.
Conclusion:

This study suggests that early prognosis after hospitalization and immunomodulation treatment for MIS-C is excellent. All 50 children treated at our institution survived, with return to functional baseline, normalized LV systolic function, and resolved coronary abnormalities. None of our patients had treatment complications such as secondary infections or bleeding from anticoagulation. CMRI in select high-risk patients revealed no persistent inflammation or scarring. This suggests an uncomplicated course of myocarditis in MIS-C with favorable outlook on long-term prognosis. However there was persistence of echocardiographic diastolic dysfunction in a few patients of uncertain significance. Larger studies are needed to aid in improved understanding of this syndrome. Meanwhile, these findings may provide guidance to clinicians particularly in relation to clinical management, outpatient monitoring, and considerations for sports clearance.

References


Table 1. Demographics, clinical characteristics and hospital course

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<th>Demographic Characteristics</th>
<th>Value</th>
<th>%</th>
<th>IQR</th>
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<tbody>
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<td>Patients, n</td>
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<td></td>
<td></td>
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<tr>
<td>Age, years, median, IQR</td>
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<td></td>
<td>5.4-11.5</td>
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<tr>
<td>Age, range</td>
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<td></td>
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<td>44%</td>
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<td><strong>Race</strong></td>
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<tr>
<td>Black, n, %</td>
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<td>Asian, n, %</td>
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<td>Non-Hispanic, n, %</td>
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<td>74%</td>
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<td><strong>Clinical Characteristics</strong></td>
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<td><strong>Weight status categories</strong></td>
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<td>Underweight (&lt;5th %ile), n, %</td>
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<td>6%</td>
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<td>Normal weight (5th-&lt;85th %ile), n, %</td>
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<td>42%</td>
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<td>Overweight (85th-&lt;95th %ile), n, %</td>
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<td>Obese (&gt;=95th %ile), n, %</td>
<td>20</td>
<td>40%</td>
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<td><strong>Hospitalization</strong></td>
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<td>79%</td>
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<td>4, 8</td>
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<tr>
<td>Discharged alive, n, %</td>
<td>50</td>
<td>100%</td>
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<td><strong>Laboratory Results</strong></td>
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<td>White blood cell count, K/uL, median, IQR</td>
<td>9</td>
<td>7.1-12.5</td>
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<td>Absolute lymphocyte count, K/uL, median, IQR</td>
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<td>Lymphopenia, n, %</td>
<td>38</td>
<td>76%</td>
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<td>Hemoglobin, g/dL, median, IQR</td>
<td>11.4</td>
<td>10.5-12.1</td>
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<td>Platelet count, K/uL, median, IQR</td>
<td>172</td>
<td>122-232</td>
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<td>122, 291</td>
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<td>High Troponin, n%</td>
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<td>38%</td>
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<tr>
<td>Medications for MIS-C</td>
<td>n</td>
<td>%</td>
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<td>IVIG, n, %</td>
<td>48</td>
<td>96%</td>
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<td>Methylprednisolone, n, %</td>
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<td>70%</td>
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<tr>
<td>Any Biologic, n, %</td>
<td>13</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Anakinra, n, %</td>
<td>6</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab, n, %</td>
<td>4</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Infliximab, n, %</td>
<td>3</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Aspirin, n, %</td>
<td>46</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin, n, %</td>
<td>23</td>
<td>46%</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Echocardiographic abnormalities present on admission and on-follow up at 2 weeks, 8 weeks and 6 months.

<table>
<thead>
<tr>
<th>Echocardiogram Findings</th>
<th>Acute (n=50)</th>
<th>2 weeks (n=47)</th>
<th>8 weeks (n=42)</th>
<th>6 months (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any coronary abnormality (n, %)</td>
<td>26 (52%)</td>
<td>13 (27%)</td>
<td>5 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>LMCA z score</td>
<td>0.38 ± 1.1</td>
<td>-0.14 ± 0.92</td>
<td>-0.40 ± 0.88*</td>
<td>-0.41 ± 0.92*</td>
</tr>
<tr>
<td>LAD z score</td>
<td>0.62 ± 1.24</td>
<td>-0.21±1.12</td>
<td>-0.85 ± 0.82*</td>
<td>-0.84 ± 0.72*</td>
</tr>
<tr>
<td>RCA z score</td>
<td>-0.14 ± 1.25</td>
<td>-0.48 ± 0.84</td>
<td>-0.77 ± 0.76*</td>
<td>-0.99 ± 0.78*</td>
</tr>
<tr>
<td>LAD/RCA Z-score &gt;= 2.5, n, %</td>
<td>8(16%)</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LAD/RCA Z-score 2-2.49, n, %</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lack of tapering (Z score &lt;2), n, %</td>
<td>14 (28%)</td>
<td>10 (21%)</td>
<td>5 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Any left ventricular (LV) systolic dysfunction, n, %</td>
<td>26 (52%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LVEF (mean, SD)</td>
<td>54 ± 9</td>
<td>64 ± 4</td>
<td>62 ± 4*</td>
<td>62 +/- 3*</td>
</tr>
<tr>
<td>Mild (LVEF 45-54%), n, %</td>
<td>15 (30%)</td>
<td>1 (20%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate (LVEF 35-44%), n, %</td>
<td>11 (22%)</td>
<td>0%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe (LVEF &lt;35%), n, %</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diastolic Dysfunction, n, %</td>
<td>16 (32%)</td>
<td>5 (11%)</td>
<td>4 (9%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

* Significant difference (p<0.05)
Figure 1

Image showing left ventricular ejection fraction (LVEF) serially improving from admission to the 6-month follow up. Red horizontal line indicates lower limit of normal (EF of 55%).
Figure 2

Temporal changes in mean coronary artery size (from left to right- left main, left anterior descending, and right coronary artery) from admission to the 6-month follow up. All coronaries have smaller absolute size by 8 weeks. Red horizontal line indicates upper limit of normal (z score > 2).
Arrival to ED with Fever above 38°C for ≥ 4* days (*may consider less days with high suspicion) AND One or more of:
- Headache/irritability
- Conjunctivitis
- Gastrointestinal symptoms (includes enteritis on imaging)
- Rash/Swollen hands and feet

Send: CBC/Diff, CMP, CRP, BNP, Troponin, Procalcitonin, Ferritin, D-dimer, Fibrinogen, PT/PTT/INR, LDH, COVID PCR, COVID Serology, Blood culture, RVP

Perform EKG, Obtain risk factors for TB

Multi-system Inflammatory Syndrome in Children (MIS-C) = Fever + Inflammation (elevated CRP and/or Ferritin) + One of the following 4 options:

**Cardiogenic and/or Distributive Shock with Single or Multi-organ Failure.**
- Fluid refractory hypotension and/or Abnormal Echo
- And/or AKI
- And/or Liver injury
- And/or Oxygen requirement

**Incomplete Kawasaki Disease**
- At least 2 clinical criteria + At least 3/6 of: Anemia for age, WBC > 15000, Elevated ALT, Plat > 450 or < 100, Albumin < 3, Sterile pyuria > 10 WBC/field OR
- At least 2 clinical criteria + Abnormal Echo (↓LVEF, CA dilation*, carditis)

**Classic Kawasaki Disease**
- At least 4/5 of: vasculitic rash, palm/sole swelling, non-exudative b/l conjunctivitis, cervical lymphadenopathy (≥ 1.5 cm), red cracked lips and/or oral/ pharyngeal mucosa erythema, strawberry tongue

**Category 4 / Observation**
- Children who do not fit into any category, though have abnormal labs. Observe clinically and trend labs in consultation with Pediatric Infectious Disease (and Pediatric Cardiology, if needed). May admit to floor and re-enter algorithm below as indicated.

**Fever > 24 hr after completion of IVIG infusion**
- Obtain CRP, Ferritin, ECHO
- If ferritin < 800 and no change in ECHO, give infliximab 5 mg/kg/dose x1
- If ferritin > 800 or worsening ECHO, give Anakinra 2.5 mg/kg/dose SC (max 100mg) q6h

**Shock Present (Fluid refractory hypotension) or ECHO with ↓LVEF or carditis**
- Admit to PICU

**High Risk KD**
- IVIG 2 gm/kg
- Aspirin 5 mg/kg/dose daily (max 81mg/dose)
- Methylprednisolone 1mg/kg IV q12h (max 60 mg/dose)
- Enoxaparin per hematology

**Low Risk KD**
- IVIG 2 gm/kg
- Aspirin 15 mg/kg/dose q6h (max 975 mg/dose)

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**See Next page for continued**

This document is intended as a general guideline. The healthcare professional must use the appropriate judgment dependent on the particular clinical situation.
Continued Care after Initial Treatment

1. Continue methylprednisolone
   a. After 24-48 hours without fever, decrease methylprednisolone to 1 mg/kg/dose IV (max 60 mg/dose) q12h
   b. May change to oral prednisone with resolution of fever for > 24 hours (1:1 conversion)
   c. Upon discharge home, prescribe prednisone 1 mg/kg/dose PO (max 30 mg) q12hr
   d. Do not taper steroid dose prior to first outpatient appointment with infectious disease
2. Continue Anakinra – Every 6 hours for 1-3 days, every 12 hours for 1-3 days, every 24 hours for 1-3 days
3. Patient may be discharged once afebrile for 24-36 hours and CRP < 50% of peak value (in infants, CRP should normalize)
3. Outpatient
   a. Schedule an appointment with ID within 5-7 days of discharge.
   b. Obtain CBC, CRP, ESR, and if elevated at discharge: ferritin, BNP, d-dimer, fibrinogen, PT/PTT/INR

Lab Schedule

- All patients should have an initial CBC/diff, CMP, CRP, ESR, Procalcitonin, troponin, BNP, CK, ferritin, d-dimer, LDH, PT/PTT/INR, fibrinogen, COVID PCR, COVID serology, blood culture, RVP, ROTEM
- Consider ADAMTS13, antithrombin-3, C3, C4, Cytokine panel, Factor 8 assay, IgG subsets, T-cell subsets, von Willebrand activity, von Willebrand antigen
- With hypotension send blood gas sampling, lactate on admission
- Second COVID PCR should be sent 12 hours after admission.

Daily Labs
- CBC/diff, CRP, ferritin, d-dimer, fibrinogen, BMP (LFT’s with liver injury), Troponin (if abnormal, as per cardiology)
- Every other day: BNP
- ROTEM as needed

Cardiology Consult Indications

Urgent:
- Hemodynamic compromise (hypotension/tachycardia out of proportion of fever) OR
- Significant arrhythmia OR
- Elevated cardiac biomarkers (Troponin beyond indeterminate and/or elevated pro-NT-BNP)

Non-Urgent:
- KD presentation without hemodynamic compromise OR
- Other arrhythmia on telemetry OR
- Other arrhythmia on telemetry OR
- Other clinical concern

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