RESEARCH ARTICLE

Multisystem inflammatory syndrome in children related to COVID-19: A New York City experience

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Abstract
In December 2019, the 2019, a novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first emerged in Wuhan, China. This has now spread worldwide and was declared a pandemic by March 2020. Initially, the pediatric population was described as a low risk for severe COVID-19. However, reports have emerged recently of cases of COVID-19 in children with a systemic inflammatory disease, with features that overlap with Kawasaki disease (KD). We describe the first 15 cases with the multisystem inflammatory syndrome in children (MIS-C), temporally related to COVID-19, who presented for care to a tertiary pediatric referral center in New York City. We discuss the disproportionate burden of disease among Hispanic/Latino and Black/African American ancestry, the distinct cytokine signature across the disease spectrum (IL-1/IL-6), and the potential role and pathogenesis of SARS-CoV-2 in this new clinical entity.

KEYWORDS
COVID-19, hyperinflammatory syndrome, Kawasaki disease, SARS-CoV-2

1 INTRODUCTION

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first emerged in Wuhan, China, and on 11 March 2020, coronavirus disease 2019 (COVID-19), the disease caused by this novel virus, was declared a pandemic. Since then, most reports have described the pediatric population as low risk for severe COVID-19. An early retrospective study evaluating pediatric outcomes in 46 pediatric hospitals North America reported that between 3 March and 14 April 2020, only 48 children required admission to a pediatric intensive care unit (PICU).1 However, on 27 April 2020, The Pediatric Intensive Care Society of the United Kingdom released an alert regarding an increased number of children presenting with multisystem inflammatory disease, with disease features that overlap with Kawasaki disease (KD) and toxic shock syndrome, many of whom had tested positive for COVID-19.

On 4 May 2020, the New York State Department of Health (NYSDOH) reported an initial 15 cases with symptoms similar to those described, and by 17 May 2020, 145 suspected cases had been reported among hospitals in New York State.

Here, we describe the first 15 cases with the multi-system inflammatory syndrome in children (MIS-C), temporally related to COVID-19, who presented for care to a tertiary pediatric referral center in New York City. We discuss the disproportionate burden of disease among Hispanic/Latino and Black/African American ancestry, the distinct cytokine signature across the disease spectrum (IL-1/IL-6), and the potential role and pathogenesis of SARS-CoV-2 in this new clinical entity.

2 METHODS

This study is a retrospective chart review of patients with suspected MIS-C related to COVID-19, admitted to the Mount Sinai Hospital in New York City, between 24 April and 19 June 2020. The study
protocol was reviewed and approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

Criteria for inclusion in the study were based on the case definition for surveillance posted by the Centers for Disease Control and Prevention Emergency Preparedness and Response and New York City Health Department, and are summarized in Table 1. For patients who met criteria, we collected demographic data, past medical history, clinical symptoms, physical examination findings, and results of imaging, cardiac, and laboratory testing performed at presentation and throughout the hospital admission. We also gathered information about the complications, outcomes, and length of hospital stay.

Initial evaluation at admission included a chest radiograph (CXR) and an electrocardiogram (EKG). A trans-thoracic echocardiogram (TTE) was performed if indicated based on EKG results. All patients were evaluated by molecular testing of nasopharyngeal specimens in universal transport media for SARS-CoV-2 (SARS-CoV-2 test, cobas 6800 system, Roche Diagnostics) and other respiratory pathogens (FilmArray Respiratory Panel 2, BioMerieux), SARS-CoV-2 antibody assay (COVID-19 antibody), and cultures of blood and urine. A cytokine panel was performed upon admission to determine interleukin (IL-1β, IL-6, IL-8) and tumor necrosis factor (TNF) levels. Other laboratory evaluation included daily monitoring of the serum inflammatory markers, C-reactive protein (CRP) and ferritin; the coagulation parameters prothrombin time, international standardized ratio, and D-dimer; brain natriuretic peptide (BNP), creatinine kinase-MB, troponin I; comprehensive metabolic panels, and a complete blood count with differential leukocyte count.

Patients who met criteria for KD, or who had any evidence of myocardial injury, were treated with high dose intravenous immunoglobulin (IVIG) plus acetylsalicylic acid (ASA). Patients with hemodynamic instability or rapid clinical decompensation also received immunomodulatory therapy with Tocilizumab (a monoclonal antibody against IL6) or Anakinra (IL1 receptor antagonist). Remdesivir was given to patients who met the criteria for compassionate use established by the sponsor (Gilead Sciences, Inc).

### Table 1 Inclusion criteria

| Inclusion criteria                                                                 | Definition                                      |
|-----------------------------------------------------------------------------------|-------------------------------------------------|
| ≥ 1 d of subjective or measured fever (≥100.4°F/38°C)                              | AND                                             |
| Hospitalization                                                                   | AND                                            |
| Age ≤ 21 yr-old                                                                   | ≤ 1 of the following                            |
| Elevated inflammatory parameters                                                   | • CRP                                          |
|                                                                                   | • ESR                                          |
|                                                                                   | • PCT                                          |
|                                                                                   | • LDH                                          |
|                                                                                   | • Ferritin                                     |
|                                                                                   | • Fibrinogen                                    |
|                                                                                   | • D-dimer                                       |
| AND ≥ 1 of the following                                                          | • New or increased oxygen requirements, imaging findings suggestive of any infectious process and/or lung injury |
| End organ damage                                                                  | • Shock (hypotension, tachycardia)              |
|                                                                                   | • Heart injury (elevated CKMB, troponins, BNP; changes in EKG and/or echocardiogram) |
|                                                                                   | • Kidney injury (decreased urine output, the elevation of Cr/BUN) |
|                                                                                   | • Liver injury (elevation of LFTs, PT, PTT)     |
|                                                                                   | • CNS involvement (history of seizures or AMS, focal deficits, and/or head imaging abnormalities) |
| AND ≥ 1 of the following                                                          | Evidence COVID-19                               |
|                                                                                   | • Confirmed SARS-CoV-2 infection                |
|                                                                                   | (nasopharyngeal RT-PCR or antibody assay)       |
|                                                                                   | AND/OR                                          |
|                                                                                   | • History of exposure to a household contact diagnosed with COVID-19 |

Abbreviations: AMS, altered mental status; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CKMB, creatine kinase myocardial band; CNS, central nervous system; Cr, creatinine; CRP, C-reactive protein; EKG, electrocardiogram; ESR, erythrocyte sedimentation rate; LFTs, liver functions tests; LDH, lactic dehydrogenase; PCT, procalcitonin; PT, prothrombin time; PTT, partial thromboplastin time; RT-PCR, reverse transcription-polymerase chain reaction test.

### 3 | RESULTS

#### 3.1 | Demographic and clinical features

Between 24 April and 14 May 2020, 15 patients age 3–20 years old (mean 12 years) who presented with suspected MIS-C secondary to SARS-CoV-2 infection were admitted to the Mount Sinai Hospital. The clinical features of these cases at presentation are detailed in Table 2. Eleven patients (73%) were male and four (27%) female. More than half (10 patients, 66%) identified as Hispanic or Latino, in comparison to 25% of overall pediatric cases admitted to our hospital over the period April 1, 2020 through 1 June 2020.

Eleven patients had no known underlying medical conditions; four patients had asthma, and one had hypothyroidism and non-alcoholic fatty liver disease. Four patients (27%) reported having an acute febrile or respiratory illness during the 4 weeks preceding hospitalization, and two had been previously diagnosed with SARS-CoV-2 infection confirmed by a positive molecular test from a nasopharyngeal swab specimen. Three patients (20%) reported prior contacts with sick household members, one of whom had confirmed SARS-CoV-2 infection.

Symptoms at presentation included fever in all patients. Of note, 13 patients (87%) had gastrointestinal complaints including vomiting, abdominal pain, and diarrhea. Respiratory symptoms were less common; only three patients complains of cough or dyspnea, and
| Patient | Gender | Age, y | Race/ethnicity | Weight (BMI) | Comorbidities | Initial presentation | Findings at PICU referral | Organ support |
|---------|--------|--------|---------------|-------------|---------------|---------------------|--------------------------|--------------|
| 1       | F      | 12     | Hispanic or Latino | 32 kg; 15 kg/m² | None | 7 d of fever (>102 F), abdominal pain, fatigue, diarrhea, emesis | BP 81/48 mm Hg; HR 164 beats/min; RR 51 breaths per min; work of breathing; SatO₂ 97% SVIA | NIV          |
| 2       | M      | 14     | Hispanic or Latino | 69 kg; 22 kg/m² | None | 4 d of fever (>103 F), abdominal pain, diarrhea, emesis, chest pain | BP 107/74 mm Hg; HR 110 beats/min; RR 19 breaths per min; SatO₂ 98% SVIA | None         |
| 3       | F      | 14     | Non-Hispanic African American | 78 kg; 29 kg/m² | None | 5 d of fever (>105 F), abdominal pain, headache, myalgia, emesis | BP 73/52 mm Hg; HR 117 beats/min; RR 26 breaths per min; SatO₂ 98% SVIA | NIV          |
| 4       | M      | 5      | Unknown | 16 kg; 12 kg/m² | None | 3 d of fever, cough, abdominal pain, nausea, vomiting | BP 82/55 mm Hg; HR 141 beats/min; RR 35 breaths per min; work of breathing; SatO₂ 100% FiO₂ 100% | VA ECMO, MV |
| 5       | M      | 6      | Hispanic or Latino | 37.7 kg; 30 kg/m² | Moderate persistent asthma | 2 d of fever (>104 F), emesis, rash | BP 107/55 mm Hg; HR 152 beats/min; RR 40 breaths per min; work of breathing; SatO₂ 96% RA | None         |
| 6       | F      | 11     | Hispanic or Latino | 43 kg; 18 kg/m² | None | 5 d of fever (>103 F), sore throat, emesis, rash, abdominal pain, red lips and red eyes | BP 74/45 mm Hg; HR 160 beats/min; RR 24 breaths per min; work of breathing; SatO₂ 100% SVIA | None         |
| 7       | M      | 17     | Hispanic or Latino | 66 kg; 20 kg/m² | None | 4 d of fever, chest pain, sore throat | BP 114/70 mm Hg; HR 73 beats/min; RR 9 breaths per min; work of breathing; SatO₂ 100% SVIA | NIV         |
| 8       | F      | 3      | Hispanic or Latino | 18 kg; 15 kg/m² | None | 6 d of fever (>103 F), emesis, diarrhea, rash, sore throat | BP 101/55 mm Hg; HR 140 beats/min; RR 48 breaths per min; SatO₂ 100% SVIA | None         |
| 9       | M      | 10     | Non-Hispanic White | 29 kg; 14 kg/m² | Asthma | 5 d of fever (>102 F), emesis, diarrhea, rash | BP 70/35 mm Hg; HR 104 beats/min; RR 28 breaths per min; SatO₂ 96% SVIA | None         |
| 10      | M      | 12     | Hispanic or Latino | 46 kg; 17 kg/m² | None | 2 d of fever (>103 F), abdominal pain | BP 91/51 mm Hg; HR 148 beats/min; RR 22 breaths per min; SatO₂ 96% SVIA | None         |
| 11      | M      | 20     | Hispanic or Latino | 60 kg; 20 kg/m² | None | 3 d of fever (>100.9 F), emesis, diarrhea, abdominal pain neck pain | BP 81/52 mm Hg; HR 133 beats/min; RR 27 breaths per min; SatO₂ 98% NV | MV          |
| 12      | M      | 20     | Hispanic or Latino | 105 kg; 33 kg/m² | Asthma | 5 d of fever (>102.5 F), dyspnea, cough, rash | No PICU admission | NIV          |
| 13      | M      | 13     | Non-Hispanic African American | 63 kg; 25 kg/m² | Hypothyroidism, NAFLD | 6 d of fever (>104 F), emesis, diarrhea, rash, abdominal pain, red eyes | BP 96/50 mm Hg; HR 119 beats/min; RR 20 breaths per min; SatO₂ 98% SVIA | MV          |
| 14      | M      | 5      | Hispanic or Latino | 21 kg; 16 kg/m² | Asthma | 3 d of fever, emesis, abdominal pain, scrotal pain, red eyes | BP 76/48 mm Hg; HR 122 beats/min; RR 36 breaths per min; SatO₂ 97% SVIA | NIV         |
| 15      | M      | 20     | Non-Hispanic White | 79 kg; 23 kg/m² | None | 3 d of fever, headache, neck stiffness, nausea, emesis, diarrhea | BP 83/45 mm Hg; HR 137 beats/min; RR 18 breaths per min; SatO₂ 10% SVIA | None         |

**Abbreviations:** BMI, body mass index; BP, blood pressure; F, female; FiO₂, fraction of inspired oxygen; HR, heart rate; M, male; MV, mechanical ventilation via endotracheal tube; NIV, noninvasive ventilation; NAFLD, nonalcoholic fatty liver disease; PICU, pediatric intensive care unit; RA, room air; RR, respiratory rate; SatO₂, oxygen saturation; SVIA, self-ventilating in air; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.
two additional patients complained of chest pain. Just under half of the patients presented with some features consistent with KD, including rash in seven (47%), conjunctivitis in four (27%), and swollen hands and feet in four (27%) cases. Tachycardia and hypotension were noted in 13 (87%) patients, and nine (60%) patients required inotropic or vasopressor support.

3.2 | Diagnosis of SARS-CoV-2 infection

COVID-19 infection was diagnosed by a positive SARS-CoV-2 PCR test from a nasopharyngeal or lower respiratory specimen during hospital admission in seven (47%) patients, or during the month before admission in an additional two (13%) patients. COVID-19 antibodies were detected in all 15 patients using a laboratory-developed test for against recombinant SARS-CoV-2 spike proteins under a Food and Drug Administration Emergency Use Authorization. This assay is able to detect a strong signal response specifically from IgG3, IgM, and IgA serum levels.4

3.3 | Imaging and other initial laboratory findings

Thirteen patients (87%) showed features of severe cardiac involvement, including an abnormal TTE in 12 (80%) and elevated serum troponin or BNP in 13 (87%). The most common findings are summarized in Table 3. Four (27%) patients presented with only depressed left ventricular function, and three (20%) with depressed biventricular function. Three patients presented with coronary artery abnormalities, including one patient with dilation and two (13%) with ectasia. One patient had ventricular tachycardia and ventricular ectopy, and another one had diffuse segment (ST) elevations on EKG. Transesophageal ecocardiography findings were improved in all patients before discharge home.

Initial CXRs demonstrated nonspecific findings such as progressive lung opacities or ground-glass opacities in seven (47%) patients. Four (27%) had reactive airway disease and four (27%) had pleural effusions. Three (20%) patients had persistently normal CXR findings throughout admission.

At admission, lymphopenia was present in 13 (87%) patients, thrombocytopenia in six (40%), hypoalbuminemia in eight (53%), and elevated fibrinogen in 14 (93%) patients. During admission, inflammatory markers were elevated in all patients, including 15 (100%) with elevated CRP and D-dimer, and 13 (87%) with elevated ferritin levels and 14 (93%) erythrocyte sedimentation rate (ESR). Procalcitonin levels were checked in 13 patients and were elevated in nine (60%) cases. Levels of both interleukin-6 (IL-6) and interleukin-8 (IL-8) were markedly elevated in all 15 (100%) patients. In contrast, tumor necrosis alpha (TNF-alpha) was only minimally elevated, in only 11 (73%) patients; no patients had elevated levels of interleukin-1 (IL-1). Of note, IL-6 and IL-8 levels were only performed on admission and not repeated. As IL-6 drives the elevation of CRP, CRP levels reflected IL-6 values. Moreover, CRP levels were easier to trend with results being rapid and more costly effective than IL-6. (See Table 4).

3.4 | Treatment and outcomes

Initially, all patients were treated with broad-spectrum antibiotics for possible septic shock and toxic shock syndrome; antibiotics were discontinued if blood cultures were without growth after 48 hours of incubation. In addition, all patients received prophylactic anticoagulation with Enoxaparin which continued until 2 weeks post-discharge. Only one patient was admitted to the general pediatric ward; 14 patients were admitted to an intensive care unit within 24 hours of presentation.

Three patients (20%) required intubation and mechanical ventilation, and an additional 5 (33%) patients required noninvasive mechanical ventilation. The child who died required extracorporeal membrane oxygenation (ECMO) during the 9 days of admission. Eight (53%) patients needed vasopressor and vasoactive therapy, and one patient required an intra-aortic balloon pump to treat cardiogenic shock.

Twelve (80%) patients received one to three intravenous doses of the anti-interleukin-6 (anti-IL-6) antibody tocilizumab; one of those patients also received SARS-CoV-2 convalescent plasma transfusion. The decision to repeat Tocilizumab was based on the persistent elevation of inflammatory markers and hemodynamic instability. Cytokine levels were not trended. Two patients (13%) initially received Anakinra, and 12 (80%) received high dose of IVIG. Three (20%) patients were treated with steroids. Two patients (13%) were treated with Remdesivir; one completed 5 days and the other one 9 days of treatment.

Of the initial 15 patients we describe, 9 had gradual normalization of D-dimer, BNP, and troponin levels during admission (Figure 1). Thirteen remained admitted for a range of 6 to 13 days (mean 8 days) and have had continued improvement in inflammatory parameters upon outpatient follow up. One patient expired on day 9 after admission and one remains admitted.

4 | DISCUSSION

Until late April 2020, SARS-CoV-2 infection in children was assumed to be asymptomatic or to cause mild febrile illness. Herein, we report 15 pediatric patients with COVID-19, who presented with symptoms suggestive of a multi-system, hyperinflammatory syndrome that shares many characteristics with known systemic inflammatory processes seen in childhood. This new syndrome has been termed multisystem inflammatory syndrome in children (MIS-C) related to COVID-19. Importantly, not all our patients were positive for SARS-CoV-2 by molecular testing of nasopharyngeal specimens. However, all patients were SARS-CoV-2 antibody-positive, suggesting that although this entity is triggered by COVID-19, the hyperinflammatory syndrome seen in these children is likely due to postinfectious cytokine storm, rather than a result of direct cell injury caused by viral replication.
| Patient | Imaging results | Pharmacologic treatment | Hospital length of stay; outcome |
|---------|-----------------|-------------------------|---------------------------------|
| 1       | CXR: Progressive lower lobe ground glass opacity. Echo (Hospital Day 1): Qualitatively normal biventricular size and systolic function. No pericardial effusion. EF = 58%. Echo (Hospital Day 5): Qualitatively normal right ventricular systolic function. Left ventricular systolic function is low normal. EF = 50%. Posterior pericardial effusion and left pleural effusion. | Vancomycin, Cefepime, Metronidazole, IVIG, Tocilizumab, Enoxaparin | 7 d; alive |
| 2       | CXR: Normal. Echo (Hospital Day 2) No ectasia or aneurysms in the visualized coronary arteries. Mild TVR. Trivial MVR. Normal right ventricular systolic function. Mildly dilated left ventricle. Normal left ventricular systolic function. EF = 58%. | IVIG, tocilizumab, enoxaparin, Clindamycin | 7 d; alive |
| 3       | CXR: Progressive lung opacities. EKG: Prolonged QTC, ventricular tachycardia. Echo (Hospital Day 1): Limited study. Qualitatively normal biventricular function. No pericardial effusion. EF not available. Echo (Hospital Day 4): Moderate TVR. Mild MVR. Qualitatively low normal right ventricular function, mild right ventricular hypertrophy. Left ventricular systolic function mildly depressed. EF = 48%. No pericardial effusion. Frequent ventricular ectopy. Echo (Hospital Day 7): Normal right ventricular function. Normal left ventricular function. EF = 52%. No pericardial effusion. | Norepinephrine, Vasopressin, Amiodarone, Lidocaine, Vancomycin, Meropenem, Anakinra, Tocilizumab, Remdesivir, Enoxaparin | 13 d; alive |
| 4       | CXR: Progressive lung opacities and pleural effusion. Echo: (Hospital Day 1): Severely depressed biventricular systolic function. Mild TVR. Trivial posterior pericardial effusion. No EF. Echo (Hospital Day 4): Mild MVR. Significantly improved right ventricular function, normal. Mildly dilated left ventricle. Left ventricular systolic function low normal, improved. EF = 50%. CT Head: Near total right middle cerebral artery infarction involving cortex, subcortical white matter and deep gray matter, left frontal subarachnoid hemorrhage. | Vancomycin, Meropenem, Cefazolin, Dopamine, Norepinephrine, enoxaparin, Vasopressin, Tocilizumab, Milrinone, Epinephrine | 9 d; demise (middle cerebral artery infarction, left frontal subarachnoid hemorrhage) |
| 5       | CXR: Normal. Echo (Hospital Day 2): No aneurysms or pericardial effusion. Left ventricular systolic function is low normal. EF = 57%. Qualitatively normal right ventricular function. CTA/Doppler upper extremities (Hospital Day 5): Normal | IVIG, Ceftriaxone, Tocilizumab | 5 d (still admitted); alive |
| 6       | CXR: Mild peri-bronchial thickening throughout the lungs. Echo (Hospital Day 2): No aneurysms or ectasia of visualized CA. Mild TVR. Trivial MVR. Normal right ventricular function, normal left ventricle systolic function. EF = 58%. Trivial pericardial effusion and trivial right pleural effusion. | Cefepime, Vancomycin, Dopamine, Norepinephrine, Enoxaparin, IVIG, Tocilizumab | 7 d; alive |
| 7       | CXR: No cardiopulmonary disease. EKG: Diffuse ST elevations. Echo (Hospital Day 1): Trivial TVR and MVR. Left ventricle systolic function mildly depressed. Normal right ventricular systolic function. No evidence of CA dilation. Trace | Enoxaparin, IVIG | 7 d; alive |
| Patient | Imaging results                                                                 | Pharmacologic treatment                                                                 | Hospital length of stay; outcome |
|---------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------|
| 8       | CXR: No cardiopulmonary disease. Echo (Hospital Day 1): Normal biventricular systolic function. Mild MVR. Normal right ventricular function. EF = 58%. | Cefepime, Linezolid, IVIG, Tocilizumab, Enoxaparin                                       | 6 d; alive                      |
| 9       | CXR: Small bilateral pleural effusions, ill-defined airway opacities. Echo (Hospital Day 1): Mild TVR and MVR. Normal right ventricular function. EF = 51%. Prominent CA, but measurements within normal limits. Slightly ectatic LAD. Trivial pericardial and pleural effusion. Echo (Hospital Day 5): Mild proximal LAD dilation. No aneurysms of CA. Trivial TVR and MVR. Normal right ventricular function. Low normal left ventricular function, improved. EF = 62%. No pericardial or pleural effusions. TVR and MVR reduced. | Dopamine, norepinephrine, Cefepime, Linezolid, IVIG, Tocilizumab, Enoxaparin, Remdesivir | 8 d; alive                      |
| 10      | CXR: Reactive airway disease. Echo (Hospital Day 2): Mild proximal LMCA ectasia. No aneurysm. Low normal left ventricular function. EF = 52%. Normal right ventricular systolic function. No pericardial or pleural effusion. Echo (Hospital Day 4): Normal left ventricular function. EF = 59%. Trivial MVR. Normal right ventricular function. No pericardial or pleural effusion. Decreased dimension of LMCA. | Cefepime, Linezolid, Flagyl, IVIG, Tocilizumab, Enoxaparin, aspirin | 8 d; alive                      |
| 11      | CXR: Progressive lung opacities and pleural effusions. Echo (Hospital Day 1): Left ventricular systolic function severely depressed. EF = 29%. Mild MVR and moderate TVR. Moderately depressed right ventricular systolic function. No pericardial effusions. Trivial bilateral pleural effusion. Echo (Hospital Day 2) Severey depressed left ventricular systolic functions. EF = 25%. Decreased right ventricular function. Mild MVR and TVR. Minimal pericardial effusion. Echo (Hospital Day 3): Moderately decreased left ventricular systolic function. EF = 40%. Decreased right ventricular function. Minimal MVR and mild TVR. Minimal pericardial effusion. Echo (Hospital Day 8): Borderline left ventricular systolic function. EF = 50%. Probable normal right ventricular function. No evidence of pericardial effusion. | Dobutamine, epinephrine, Tocilizumab, Enoxaparin, Convalescent plasma, methylprednisolone | 13 d; alive                     |
| 12      | CXR: Right middle lobe opacity. Echo: Not done.                                                                 | Cefepime, Linezolid, IVIG, Tocilizumab, Enoxaparin                                        | 4 d; alive                      |
| 13      | CXR: Progressive lung opacities. Echo (Hospital Day 1): Mildly diffusely ectatic left main and LAD. Left prominent circumflex. No aneurysms. Moderate TVR. Mildly depressed right | Dopamine, norepinephrine, Meropenem, Linezolid, IVIG, Anakinra, Tocilizumab, Enoxaparin, Aspirin | 10 d; alive                     |
This novel entity appears to share some features with KD, and as in the development of KD, infection appears to trigger a dysregulated immune response in genetically predisposed individuals. However, although KD and MIS-C share many similarities, they differ in several important ways. First, the complete clinical picture is distinct, as evidenced by our patients. Less than half of our patients had any symptoms of KD, and none had all of them. Furthermore, our patients had abdominal and cardiac symptoms that were atypical for KD. Finally, while many patients had evidence of mild coronary artery dilation, despite their severe inflammatory picture, none had major coronary artery findings, which would be very unusual in KD. A second important difference is that the profile of cytokines leading to the inflammatory process appears to be distinct in MIS-C and K. In patients with KD, IL-1 appears to be the main mediator of coronary artery inflammation, and IL-1 blockade has been used successfully to treat previously refractory KD cases. In contrast, MIS-C appears to be driven predominantly by IL-6 and IL-8. As in other reports of critically ill COVID-19 cases, for our patients, IL-6 levels were elevated at a presentation in all cases, in contrast to levels of IL-1, which were within the reference range.

The discordance between IL-1 and IL-6 levels is noteworthy as for many infectious and inflammatory processes, the production of IL-1 and IL-6 are linked. Several viruses have been shown to be able to increase IL-6 levels directly, either by enhanced IL-6 mRNA transcription or by stabilization of IL-6 mRNA. Also of note, the spike protein from a related virus identified in 2003, SARS-CoV, has been shown to induce increased IL-6 levels in murine macrophage and lung epithelial cell cultures. The efficacy of early determination of cytokine levels, particularly IL-6, and administration of specific antibody when indicated, in management of critically ill COVID-19 patients, has been reported for adults, and more recently for children, is consistent with our experience.

The relative absence of pulmonary findings in pediatric COVID-19 cases in comparison with adults raises additional questions regarding pathogenesis, as pulmonary involvement does not appear to be the major driver of dysfunction in SARS-CoV-2 infection in children. Findings in KD provide an interesting parallel. Previously, Brown et al demonstrated infiltration by CD45RO+ (activated or memory) T cells and cytotoxic CD8+ T cells in coronary artery aneurysms from patients with fatal acute KD coronary arteritis and concluded that this finding supported the

| Patient | Imaging results | Pharmacologic treatment | Hospital length of stay; outcome |
|---------|----------------|------------------------|-------------------------------|
| 14      | CXR: Reactive airway disease. Echo (Hospital Day 1): Qualitatively normal biventricular size and systolic function. Mildly dilated left main and proximal left anterior descending coronary arteries. No aneurysms of the visualized coronaries. Trivial posterior pericardial effusion no evidence of pleural effusion EF = 56%. Echo (Hospital Day 5): Qualitatively normal biventricular size and systolic function. Mildly dilated left main and proximal left anterior descending coronary arteries. No aneurysms of the visualized coronary arteries. Mildly dilated aortic root. Mildly dilated ascending aorta. Posterior pericardial effusion and no pleural effusion. | Norepinephrine, epinephrine, Cefepime, Clindamycin, Tocilizumab, Enoxaparin | 8 d; alive |
| 15      | CXR: Atelectasis. Echo (Hospital Day 1): Decreased left ventricular systolic function. EF = 40%. Mildly decreased right ventricular function. Mild MVR and TVR. Small pericardial effusion. Echo (Hospital Day 7) Mild left ventricular systolic dilation. EF = 45%-50%. Normal right ventricular function. Mild MVR. Small pericardial effusion. | Dobutamine, Norepinephrine, Hydroxychloroquine, Ceftriaxone, Doxycycline | 9 d; alive |

Abbreviations: CTA, computer tomography angiography; CXR, chest X-ray; Echo, echocardiography; EF, ejection fraction; LMCA, left middle circumflex artery; LV, left ventricle; MCA, middle cerebral artery; MVR, mitral valve regurgitation; RV, right ventricle; TVR, tricuspid valve regurgitation.
| Patient | Ferritin (ng/mL) | D-dimer (ug/mL) | Troponin (ng/mL) | BNP (pg/mL) | CRP (mg/L) | Procalcitonin (pg/mL) | Albumin (g/dL) | Platelets (×10^8) | SARS CoV-2 PCR | COVID-19 antibody (0.0-5.0 pg/mL) | IL-6 (0.0-220 pg/mL) | IL-8 (0.0-5.0 pg/mL) | TNF-alfa (0.0-5.0 pg/mL) | IL-1 Beta (0.0-5.0 pg/mL) | Microbiology results | Cytokine panel |
|---------|----------------|----------------|-----------------|------------|-----------|---------------------|--------------|----------------|----------------|-------------------------------|------------------|----------------|-------------------|------------------|-----------------|-----------------|
| 1       | 288            | 375            | <0.01           | 132        | 249       | 16.74               | 3.6          | 123             | ND             | Positive                       | 214.0            | 54.4           | 44.4              | 0.9              |
| 2       | 267            | 1.62           | 61              | 68.5       | 168       | 0.53                | 3.9          | 261             | ND             | Positive                       | 99.9             | 49.9           | 30.1              | 1.1              |
| 3       | 628            | 243            | 0.47            | 401        | 221       | 202                 | 3.9          | 238             | Positive         | Positive                       | 63.7             | 126.0          | 23.1              | 0.9              |
| 4       | 1187           | 17.68          | 0.06            | 3658       | 301       | 26.77               | 2.1          | 205             | ND             | Positive                       | 282              | 45             | 28                | 0.4              |
| 5       | 446            | >20            | 0.02            | 88.2       | 289       | 2.95                | 1.9          | 110             | ND             | Positive                       | 311              | 28             | 23                | 0.3              |
| 6       | 2272           | 6.2            | 0.06            | 12166      | 145       | 22.8                | 2.3          | 42              | ND             | Positive                       | 254              | 81.5           | 51.9              | 0.4              |
| 7       | 264            | 0.32           | 27.36           | 64.30      | 46.8      | 0.11                | 3.8          | 336             | Presumptive positive | Positive                       | 11.2             | 4.4            | 10.7              | 0.4              |
| 8       | 275            | 280            | 0.10            | 1202       | 390       | 0.43                | 2.6          | 516             | Presumptive positive | Positive                       | 253              | 21.6           | 19.6              | 0.3              |
| 9       | 1197           | 2.23           | 0.98            | 3068       | 284       | 11.49               | 2.1          | 140             | Positive         | Positive                       | 374              | 54             | 68                | 0.6              |
| 10      | 364            | 1.74           | 0.14            | 39         | 202       | 0.70                | 4.3          | 198             | Positive         | Positive                       | 200              | 25             | 20                | 1.5              |
| 11      | 519            | 1.91           | 2.73            | 431        | 284       | 5.45                | 3.2          | 97              | Presumptive positive | Positive                       | 343              | 37.6           | 19.5              | <0.3             |
| 12      | 1597           | 0.45           | <0.01           | <10        | 181       | 0.20                | 3.7          | 324             | Presumptive positive | Positive                       | 52.5             | 9.8            | 23.4              | <0.3             |
| 13      | 2010           | 326            | 0.02            | 120        | 363       | 0.20                | 3.1          | 205             | ND             | Positive                       | 286              | 37             | 56                | 0.1              |
| 14      | 850            | 446            | 0.05            | 72.4       | 202       | 2.35                | 3.3          | 140             | ND             | Positive                       | 504              | 149            | 49                | 1.6              |
| 15      | 10170          | 14.23          | 0.33            | 72.4       | 304       | 3.14                | 3.2          | 90              | Presumptive positive | Positive                       | 217              | 12.6           | 26.8              | <0.3             |

Abbreviations: COVID-19, coronavirus disease 2019; ND, not detected; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
presence of an intraepithelial pathogen, most likely viral, causing endothelial injury. More recently, Varga et al\textsuperscript{11} reported evidence of virus-like particles within endothelial cells and endothelitis in tissues from COVID-19 patients. Endothelial cell dysfunction due to direct viral infection could potentially explain the severe systemic impaired microcirculatory function observed in COVID-19 affected patients.

Disparities in disease outcomes following SARS-CoV-2 infection among racial and ethnic groups, and the occurrence of more severe disease, hospitalization, and death among persons of Black/African American and Hispanic/Latino have been reported.\textsuperscript{12} The clear predominance of children of Hispanic/Latino and Black/African American ancestry among our patients with COVID-associated MIS-C emphasizes the critical importance of measures to prevent virus transmission in this age group.

5 | CONCLUSIONS

MIS-C associated with COVID-19 is a severe presentation of SARS-CoV-2 infection in pediatric patients that has many overlapping features with KD. As in KD, symptoms and organ dysfunction appear to result from a hyperinflammatory response to an infectious trigger. In contrast to KD, in which elevated IL-1 plays a major role, in MIS-C, levels of IL-6 are elevated in the absence of increased IL-1. Although many questions remain, MIS-C is a newly recognized cytokine-mediated presentation of SARS-CoV-2 infection.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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