# CASE REPORT



# Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series

Kathleen Chiotos,<sup>1,2,3</sup> Hamid Bassiri,<sup>2,3</sup> Edward M. Behrens,<sup>4</sup> Allison M. Blatz,<sup>2</sup> Joyce Chang,<sup>3,4</sup> Caroline Diorio,<sup>5</sup> Julie C. Fitzgerald,<sup>1,3</sup> Alexis Topjian,<sup>1,3</sup> and Audrey R. Odom John<sup>2,3</sup>

<sup>1</sup>Division of Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; <sup>2</sup>Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; <sup>3</sup>Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; <sup>4</sup>Division of Rheumatology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; and <sup>5</sup>Division of Hematology and Oncology, Children's Hospital of Philadelphia, Philadelphia, Philadelphia, Pennsylvania, USA;

We present a series of 6 critically ill children with multisystem inflammatory syndrome in children. Key findings of this syndrome include fever, diarrhea, shock, and variable presence of rash, conjunctivitis, extremity edema, and mucous membrane changes. **Keywords.** COVID-19; Kawasaki disease, multisystem inflammatory syndrome in children; SARS-CoV-2.

On 27 April 2020, the United Kingdom National Health Service issued an alert highlighting a multisystem inflammatory syndrome increasingly observed across the United Kingdom, citing a possible link to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease it causes, coronavirus disease 2019 (COVID-19). On 6 May 2020, authors from London, England, reported clinical and laboratory features of a cluster of 8 children with hyperinflammatory shock, all of whom tested positive for SARS-CoV-2 antibodies [1]. Clinical characteristics of these cases share features with toxic shock syndrome, Kawasaki disease, and Kawasaki disease shock syndrome, including fever, shock, and variably rash, conjunctivitis, extremity edema, and gastrointestinal symptoms. On 5 May, the New York City Department of Health issued a health alert including 15 similar cases [2]. Most recently, on14 May, the Centers for Disease Control and Prevention issued a public health advisory and case definition for this hyperinflammatory syndrome, termed multisystem inflammatory syndrome in children (MIS-C) [3]. Here, we describe the clinical features, laboratory findings, and therapies for a cohort of 6 children with MIS-C cared for in our tertiary pediatric intensive care unit (PICU).

## **CASE PRESENTATIONS**

### Case 1

A 14-year-old female with no chronic medical conditions presented with a 5-day history of fever; headache; diarrhea; a

Journal of the Pediatric Infectious Diseases Society 2020;XX(XX):1–6

diffuse, erythematous rash; and a 1-day history of dyspnea. Her lowest documented blood pressure within 24 hours of admission was 79/39 mm Hg. Notable laboratory findings on admission included elevated inflammatory markers, hyperferritinemia, hyponatremia, and acute kidney injury. Nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) testing was negative (Table 1). Chest radiography demonstrated bilateral pulmonary infiltrates, and bedside cardiac ultrasound demonstrated moderately diminished left ventricular (LV) function (Table 2). She was emergently intubated and started on vasoactive infusions. SARS-CoV-2 PCR testing from tracheal aspirates were negative on 2 repeat samples. Vancomycin, cefepime, clindamycin, and doxycycline were started empirically for concern of toxic shock syndrome or rickettsial disease. Over the first 5 hospital days (HD), she had intermittent fevers and developed thrombocytopenia, mild coagulopathy, hypoalbuminemia, and leukocytosis. To evaluate for incomplete Kawasaki disease/Kawasaki disease shock syndrome, an echocardiogram was performed on HD 6 that demonstrated normal biventricular systolic function (shortening fraction [SF], 38%; normal, 28%-45%) but identified right coronary artery dilation (Boston z score, 3.15). She was then treated with intravenous immunoglobulin (IVIG) 2 g/ kg, methylprednisolone 2 mg/kg/day, and low-dose aspirin. Her fever resolved on HD 6. She was weaned off vasoactive infusions by HD 5 and was extubated on HD 6. She was transferred out of the PICU on HD 8, discharged to acute rehabilitation on HD 14, and discharged home HD 17. Her final echocardiogram on HD 13 demonstrated normal biventricular systolic function (SF, 37%) and similar right coronary artery dilation (Boston zscore, 3.32). SARS-CoV-2 immunoglobulin G (IgG) testing collected on HD 17 was positive.

# Case 2

A 12-year-old male with no chronic medical conditions presented to an outside facility with a 6-day history of fever,

Received 9 May 2020; editorial decision 22 May 2020; accepted 25 May 2020; Published online May 28, 2020.

Correspondence: Kathleen Chiotos, Roberts Center for Pediatric Research, 2716 South Street, Room 10292, Philadelphia, PA 19146 (chiotosk@email.chop.edu).

<sup>©</sup> The Author(s) 2020. Published by Oxford University Press on behalf of The Journal of the Pediatric Infectious Diseases Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com. DOI: 10.1093/jpids/piaa069

Clinical Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age in years/sex	14 F	12 M	9 F	5 F	5 F	6 F
Race/ethnicity	Black/not Hispanic or Latino	Unknown/not Hispanic or Latino	White/not Hispanic or Latino	White/not Hispanic or Latino	Unknown/not Hispanic or Latino	Black/not Hispanic or Latino
Body mass index (kg/m²)/comorbidities	18.8/none	20.5/none	14.9/none	16.0/none	19.9/none	19.4/none
Presenting symptoms						
Fever	+	+	+	+	+	+
Diarrhea	+	+	+	+	-	_
Abdominal pain/emesis	-	+	+	+	+	+
Rash	+	-	-	+	_	_
Conjunctivitis	-	-	+ <sup>a</sup>	-	+	-
Fissured lips/strawberry tongue	_	+	+ª	+	_	_
Lymphadenopathy	-	-	-	-	-	-
Extremity edema	-	-	+ª	+	_	-
Headache	+	-	-	-	-	-
Altered mental status/irritability	-	+	-	-	+	_
Respiratory failure	+	+	-	+	-	+
Shock	+	+	+	+	+	+
Key initial findings						
C-reactive protein (mg/dL)	34.3	28.8	14.7	16.8	30.7	8.3
(Ref: 0.0–0.9 mg/dL)						
Procalcitonin (ng/mL)	15.29	81.03	15.2	69.97	15.04	>100
(Ref: 0.0-0.1 ng/mL)						
Ferritin (ng/mL)	1096	1267	ND	512.6	804	768
(Ref: 13.7–78.8 ng/mL)						
Platelets (×10 <sup>3</sup> /µL)	150	161	180	98	46	217
(Ref: 150-400 × 10 <sup>3</sup> /µL)						
Lymphocyte count (cells/µL)	170	510	300	910	1200	970
(Ref: 970–3960/µL) <sup>b</sup>						
Brain type natriuretic peptide (pg/mL)	ND	2831	518ª	606	797	18 605
(Ref: 0.0–100.0 pg/mL)						
Troponin (ng/mL)	ND	0.05	0.12ª	0.30	0.56	1.39
(Ref: 0.0-0.3 ng/mL)						
Acute kidney injury <sup>c</sup>	+	+	-	_	+	+
Fever duration (during admission, days)	6	5	5	6	2	Ongoing
Cardiopulmonary support						- 5 - 5
Ventilation support	MV	NI	NI	MV	None	MV
Vasoactive support	Epi, NorEpi	Epi, Mil	-	Epi, Mil	Epi, Dopa	Epi, NorEpi, Dobut, Mi
Antiinflammatory therapies	F7 * F	1.7			F. F. F.	F . F
Number of doses of intravenous immuno- globulin (2 g/kg)	1	1	1	2	2	1
Methylprednisolone 2 mg/kg/day	+	-	+	+	+	+
Other antiinflammatory therapy	-	+ <sup>d</sup>	-	+8	_	+ <sup>f</sup>
Antibiotics (duration in days)	Van, Cfp, Cli, Dox (7)	Van, Cfp, Cli (7)	Van, P/T (2) Van, Cip (2)	Van, Cfp (2) Ctx (5)	Van, Cfp (2)	Van (1), Ctx (3), Met (1)
SARS-CoV-2 testing						
Nasopharyngeal SARS-CoV-2 PCR	Negative	Negative	Positive <sup>g</sup>	Positive <sup>g</sup>	Negative	Positive <sup>9</sup>
Tracheal aspirate SARS-CoV-2 PCR	Negative	ND	ND	Negative	ND	ND
Anti-SARS-CoV-2 immunoglobulin G	Positive <sup>h</sup>	Positive	ND	Positive	Positive	Positive
Known SARS-CoV-2 exposure						
Outcome	Home	Home	Home	Home	Home	Pediatric intensive care unit

Abbreviations: Cfp, cefepime; Cip, ciprofloxacin; Cli, clindamycin; Ctx, ceftriaxone; Dobut, dobutamine; Dopa, dopamine; Dox, doxycycline; Epi, epinephrine; F, female; M, male; Met, metronidazole; Mil, milrinone; MV, mechanical ventilation; ND, not performed; NI, noninvasive mechanical ventilation; NorEpi, norepinephrine; P/T, piperacillin/tazobactam; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; Van, vancomycin.

<sup>a</sup>Developed this feature on hospital day 5.

\*Phore are minor variations in reference range for this laboratory test based on age and sex; reference ranges for a 7.5-year-old patient (median age of cohort) provided.
\*Acute kidney injury defined as an increase in serum creatinine ≥1.5 times the upper limit of normal.

<sup>d</sup>Methylprednisolone 10 mg/kg once (prior to admission to our institution).

eMethylprednisolone 30 mg/kg daily × 3; anakinra 4 mg/kg daily. Methylprednisolone 30 mg/kg daily × 3.

 $^{\circ}\text{SARS-CoV-2}$  PCR testing positive with a high cycle threshold.

<sup>h</sup>Obtained after intravenous immunoglobulin.

Table 2.	Laboratory Features of Six Child	ren With Multisystem Inflammatory Syndrome in Children
----------	----------------------------------	--

Laboratory Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6ª
White blood cell count (×10³/µL)						
Initial	16.7	16.8	11.7	9.1	11.7	10.3
Maximum	50.1	25.5	11.7	42.8	39.2	24.5
Ref 4.3–11.0 × 10³/µL <sup>b</sup>						
Absolute lymphocyte count (cells/µL)						
Initial	170	510	300	910	1200	970
Minimum	170	510	300	250	300	320
Ref: 970–3960/µL <sup>b</sup>						
Hemoglobin (g/dL)						
Initial	12.5	11.2	12.4	11.2	11.0	9.6
Minimum	7.2	7.8	9.2	6.9	9.2	7.4
Ref 11.5–15.5 g/dL <sup>b</sup>						
Platelets (×10³/µL)						
Initial	150	175	180	98	46	217
Minimum	64	175	117	92	33	175
Ref: 150–400 × 10 <sup>3</sup> /µL						
Creatinine (mg/dL)						
Initial	2.5	0.9	0.7	0.5	1.6	3.6
Maximum	2.5	0.9	0.7	1.3	1.6	4.0
Age-based reference	Ref: 0.3–0.8	Ref: 0.2–0.5	Ref: 0.2–0.5	Ref: 0.1–0.4	Ref: 0.1–0.4	4.0 Ref: 0.1–0.5
Initial sodium (mmol/L)	125	134	132	129	131	128
Ref: 136–145 mm/L <sup>b</sup>	120	707	102	120	101	120
Alanine aminotransferase (U/L)						
(U/L) Initial	23	53	13	28	98	39
Maximum	75	53	38	20	98	108
Ref: 10–35 U/L <sup>b</sup>	75	00	30	29	30	100
C-reactive protein (mg/dL)						
Initial	34.3	28.8	14.7	16.8	30.7	8.3
Maximum	35.7	33.1	16.4	19.1	30.7	18.4
Ref: 0.0–0.9 mg/dL	30.7	33.1	10.4	19.1	30.7	10.4
Procalcitonin (ng/mL) Initial	15.00	01.00	15.20	00.07	15.04	. 100
	15.29	81.03	15.20	69.97	15.04	>100
Maximum	28.40	90.19	15.20	69.97	15.04	>200
Ref: 0.0–0.1 ng/mL						
Albumin (g/dL)	2.0	20	4.0	4.0	20	0.4
Initial	3.6	2.6	4.3	4.0	2.6	2.4
Minimum	2.2	2.2	2.8	2.6	2.1	2.4
Ref: 3.7–5.6 g/dL <sup>b</sup>						
D-dimer (µg/mL)	ND	ND	0.70	4.01	07.70	2.22
Initial	ND	ND	6.73	1.01	27.76	6.66
Maximum	ND	3.30	11.51	2.15	27.76	16.24
Ref: 0.0–0.499 µg/mL Ferritin (ng/mL)						
Initial			• 7=			
Maximum	1096.2	1267.0	ND	512.6	804.2	768.0
Ref: 13.7–78.8 ng/ml <sup>b</sup>	1096.2	1267.0	ND	748.1	804.2	1162.0
nternational normalized ratio						
Initial	1.11	1.34	1.62	1.27	1.05	1.23
Maximum	1.66	1.34	1.69	1.56	1.05	2.50
Ref: N/A						
Lactic dehydrogenase (U/L) — initial only	993	ND	ND	1059	728	885
, Ref 420–750 U/L <sup>b</sup>						

#### Table 2. Continued

aboratory Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6 <sup>a</sup>
Troponin (ng/mL)						
Initial	ND	0.05	ND	0.30	0.56	1.39
Maximum	ND	0.16	0.12	0.97	0.60	1.87
Ref: 0.0–0.3 ng/mL						
Brain type natriuretic peptide (pg/mL)						
Initial	ND	2831	ND	606.3	797.1	18 606.5
Maximum	ND	6938	517.7	1718.6	997.6	18 606.5
Ref: 0.0–100.0 pg/mL						
nitial chest radiograph findings	Diffuse bilateral infiltrates	Diffuse bilateral infiltrates	Normal	Mild peribronchial thick- ening bilaterally; right lower lung patchy opacities	Prominent cardiac silhou- ette and mild central vascular congestion	Dense bilateral airspace opacities, right greate than left, trace pleura fluid, heart appears prominent
Echocardiogram <sup>c</sup>						
Initial	Normal biventricular function (LV SF 38%), <sup>d</sup> diffuse dila- tion of right coronary artery (Boston <i>z</i> score, 3.15) <sup>e</sup>	Low normal LV function (LV SF 29%), <sup>d</sup> mildly dimin- ished RV function, no coronary artery dilation	Normal function (LV SF 37%), <sup>d</sup> no coronary artery dilation	Moderately diminished LV function (LV SF 19%), <sup>d</sup> no coronary artery dilation	Mildly diminished LV function LV SF 25%), <sup>d</sup> no coronary artery dilation	Moderate LV dilation, mildly diminished LV function (LV SF 24%), low normal RV function
Final or most recent	Normal LV and RV function (LV SF 37%). <sup>4</sup> right coronary artery dilation (Boston <i>z</i> score 3.32)	Normal LV and RV function (LV SF 35%), <sup>d</sup> no coro- nary artery dilation	Normal function (LV SF 37%), <sup>d</sup> no coronary artery dilation	Normal LV and RV function (LV SF 33%), <sup>d</sup> proximal coronaries are echo bright <sup>e</sup>	Normal LV and RV func- tion (LV SF 43%), <sup>d</sup> no coronary artery dilation <sup>c</sup>	Normal LV and RV func- tion (LV SF 35%), <sup>d</sup> no coronary artery dilation

Abbreviations: LV, left ventricle; RV, right ventricle; SF, shortening fraction.

Patient remains hospitalized at the time of this writing.

<sup>b</sup>There are minor variations in reference range for this laboratory test based on age and sex; reference ranges for a 7.5-year-old patient (median age of cohort) provided

<sup>c</sup>Limited to echocardiography performed at our institution

Normal range for SF is 28%-45%.

Bedside cardiac ultrasound on hospital day 0 demonstrated moderately diminished LV function; this echo was performed on hospital day 6.

abdominal pain, diarrhea, mucous membrane changes (fissured lips), respiratory distress, and altered mental status. Nasopharyngeal SARS-CoV-2 PCR was negative. His lowest documented blood pressure within 24 hours of admission was 60/24 mm Hg. Notable laboratory findings on admission included elevated inflammatory markers, pro-brain type natriuretic peptide (pro-BNP), and troponin (Tables 1 and 2). An echocardiogram was performed on HD 1 that by report demonstrated mild LV dysfunction, without coronary artery abnormalities. Chest radiography demonstrated diffuse bilateral infiltrates. He was started on milrinone, epinephrine, and vasopressin, as well as noninvasive mechanical ventilation. On HD 2, he received pulse dose methylprednisolone (10 mg/kg) and IVIG 2 g/kg for possible Kawasaki disease shock syndrome, then was transferred to our facility for possible extracorporeal membrane oxygenation. A repeat echocardiogram on HD 3 showed low normal LV function (SF, 29%) and mildly diminished right ventricular systolic function. His fevers resolved by HD 5 without further immunomodulatory therapies. He was weaned off inotropic infusions and noninvasive mechanical ventilation by HD 8, transferred out of the PICU on HD 9, and discharged home on HD 12. Repeat echocardiography on HD 7 and HD 9 revealed normal function (SF, 35%) and no coronary artery abnormalities. SARS-CoV-2 IgG testing obtained on HD 0 was positive.

#### Case 3

A 9-year-old female with no chronic medical conditions presented with fever, copious diarrhea, and intermittent periumbilical pain. Laboratory findings were notable for elevated inflammatory markers (Tables 1 and 2). An abdominal computed tomography (CT) scan performed for possible appendicitis demonstrated ileocolitis. Initial SARS-CoV-2 nasopharyngeal PCR testing was negative. She was admitted to the inpatient unit initially, transferred to the PICU for apparent hypovolemic shock from secretory diarrhea on HD 3, and transferred back to the inpatient unit on HD 4 after shock resolved with fluid resuscitation. Her lowest documented blood pressure within 24 hours of her PICU admission was 92/50 mm Hg. A repeat SARS-CoV-2 nasopharyngeal PCR was positive with a high cycle threshold (37.54). On HD 5, she developed conjunctivitis, extremity edema, and mucosal changes (fissured lips and strawberry tongue). An echocardiogram showed no coronary artery abnormalities and normal cardiac function (SF, 37%). She received IVIG 2 g/kg, methylprednisolone 2 mg/kg/ day, and low-dose aspirin starting on HD 5. On HD 6, her fever resolved, but she developed hypoxia and was found to have

cardiomegaly and pulmonary edema on chest radiography. She was transferred to the PICU and required noninvasive mechanical ventilation. Laboratory findings at the time of transfer were additionally notable for an elevated BNP and troponin. Her acute respiratory failure was attributed to volume overload in the setting of fluid resuscitation for hypovolemic shock and capillary leak from hyperinflammatory syndrome. She was managed supportively with furosemide, weaned off respiratory support by HD 7, and was discharged home on HD 8. SARS-CoV-2 IgG testing was not obtained.

#### Case 4

A 5-year-old female with no chronic medical conditions presented with a 4-day history of fever, morbilliform rash, mucosal changes (fissured lips), conjunctivitis, swollen hands, emesis, diarrhea, irritability, and nuchal rigidity. Her lowest documented blood pressure within 24 hours of admission was 65/32 mm Hg. Notable laboratory findings included elevated inflammatory markers, thrombocytopenia, and elevated BNP and troponin (Tables 1 and 2). Initial SARS-CoV-2 PCR testing was negative, but a repeat test on HD2 was positive, with a high cycle threshold (40.2). Her chest radiograph demonstrated peribronchial thickening with patchy right lower lobe infiltrates. She was admitted to the PICU due to hypotension and concern for shock and found to have moderately diminished LV systolic function (SF, 19%) without coronary artery abnormalities. She was started on epinephrine and milrinone infusions and was intubated. Given this constellation of findings, she received IVIG 2 g/kg and methylprednisolone 2 mg/ kg/day on HD 0. Due to ongoing fevers, IVIG 2 g/kg was repeated on HD 2. On HD 2, a lumbar puncture was performed that was consistent with aseptic meningitis with 68 white blood cells, of which 21% were neutrophils, 69% were lymphocytes, and 9% were monocytes. Cerebrospinal fluid (CSF) bacterial cultures were negative, and CSF was negative for enterovirus by PCR. A head CT performed on HD 2 showed diffuse cerebral edema; a repeat study performed 12 hours later showed improved edema. Due to ongoing fevers, elevated inflammatory markers, thrombocytopenia, and continued cardiac dysfunction, anakinra (4 mg/kg/day) and pulse methylprednisolone (30 mg/kg/day) were started on HD 4. She was weaned off epinephrine on HD 4, extubated on HD 5, and off milrinone HD 6. Her fever resolved on HD 6. An echocardiogram done on HD 5 showed normal biventricular function (SF, 33%) without coronary artery dilation. She was transferred to the inpatient care area on HD 8 and discharged home on HD 11. SARS-CoV-2 IgG testing obtained on HD 1 was positive.

#### Case 5

A 5-year-old female with no chronic medical conditions presented with a 5-day history of fever, bilateral conjunctivitis, irritability, lethargy, and nuchal rigidity. She was initially admitted to an outside facility PICU, then transferred to our institution on HD 0. Her lowest documented blood pressure within 24 hours of admission was 62/34 mm Hg. Notable laboratory findings on admission included elevated inflammatory markers, hypoalbuminemia, thrombocytopenia, and elevated and troponin (Tables 1 and 2). SARS-CoV-2 nasopharyngeal PCR was negative. Her chest radiograph demonstrated a prominent cardiac silhouette and mild central vascular congestion. Her echocardiogram demonstrated LV dilation, mildly diminished LV function (SF, 25%), and no coronary artery abnormalities. She was started on dopamine and epinephrine for cardiac support. She did not require mechanical ventilation but was tachypneic on admission. Given this constellation of findings, she received IVIG 2 g/kg on HD 0. Due to ongoing fevers, a second dose of IVIG 2 g/kg and methylprednisolone 2 mg/kg/ day was added on HD 2. She was also started on low-dose aspirin. She was weaned off inotropic support on HD 1, and her fever resolved on HD 2. Her mental status and tachypnea improved, and she was transferred to the inpatient care area on HD 3. A follow-up echocardiogram done on HD 5 showed mild LV dilation, normal biventricular function (SF, 43%), and no coronary artery dilation. She was discharged home on HD 11. SARS-CoV-2 IgG testing obtained on HD 0 was positive.

#### Case 6

A 6-year-old female with no chronic medical conditions presented with a 7-day history of fever, abdominal pain, and bilious emesis. She was initially admitted to an outside facility PICU where she was intubated and started on norepinephrine for shock and subsequently transferred to our institution on HD 1. Her lowest documented blood pressure within the 24 hours of admission was 46/18 mm Hg. Notable laboratory findings on admission included elevated inflammatory markers, hypoalbuminemia, and elevated BNP and troponin (Tables 1 and 2). SARS-CoV-2 nasopharyngeal PCR was negative at the outside facility but positive with high cycle threshold (39.17) at our institution. Her echocardiogram on HD 0 demonstrated moderate LV dilation with mildly diminished systolic shortening (SF, 24%) and low normal right ventricular systolic shortening. Dobutamine and epinephrine and, eventually, milrinone were added for cardiac support. Given this constellation of findings, she received IVIG 2 g/kg on HD 0 and methylprednisolone 2 mg/kg/day. Due to worsening thrombocytopenia, relative neutropenia, and hepatosplenomegaly suggestive of possible macrophage activation syndrome, she received pulse steroids (30 mg/kg/day) on HD 1-3. Her fever resolved by HD 1, she was weaned off epinephrine and dobutamine by HD 4, and was extubated on HD 7. Multiple echocardiograms were subsequently performed demonstrating moderate LV dysfunction (SF, 16%-25%). Of note, she also developed intermittent

premature ventricular contractions, bigeminy, and trigeminy. By HD 7, her LV function normalized (SF, 35%) and no coronary artery dilation was noted. She remains hospitalized in the PICU at the time of writing this report. SARS-CoV-2 IgG testing obtained on HD 0 was positive.

# DISCUSSION

The recent emergence of SARS-CoV-2 in humans and the resulting pandemic of COVID-19 is an ongoing global health crisis. One of the most unique features of this disease is its relatively benign course in pediatric populations [4, 5] despite high levels of nasopharyngeal viral RNA of SARS-CoV-2–infected children, suggesting a permissive state for viral replication [6]. However, since late April 2020, there have been an increasing number of worldwide reports of children with MIS-C, which, in addition to persistent fever, diarrhea, and variably rash, conjunctivitis, and extremity edema, appears to often be associated with severe illness including shock and myocardial dysfunction [1–3].

The current case series supports this syndrome as a clinical entity potentially driven by a disordered immunological response following SARS-CoV-2 infection. Evidence of prior infection includes positive antibody testing for SARS-CoV-2 IgG antibodies in all but 1 patient (who was not tested) and weakly positive SARS-CoV-2 nasopharyngeal PCRs in 3 patients. None of these patients had a close contact with a documented SARS-CoV-2 infection, though these cases presented several weeks after the start of documented community transmission of SARS-CoV-2 in our region. Despite the constellation of symptoms and signs that resemble features of Kawasaki disease, there are several features that may distinguish this syndrome based on ours and the other published series, including prominent cardiac dysfunction with troponin leak and extremely elevated BNPs; frequent, often severe, enteropathy (8/8 in the prior series, 4/6 in the present series, in contrast to 15%-26% of patients diagnosed with Kawasaki disease prior to the COVID-19 pandemic) [7, 8]; and relative thrombocytopenia instead of thrombocytosis, as seen with hyperinflammatory states such as macrophage activation syndrome and Kawasaki disease shock syndrome (3/8 in the prior series, 3/6 in the present series) [1]. Further, for some patients, fever and gastrointestinal symptoms preceded the development of other "classic" clinical features of Kawasaki disease, including rash, conjunctivitis, mucous membrane changes, and extremity edema, which were variably present in our cohort.

While the clinical features of our cohort are consistent with the prior case series [1], we additionally highlight 2 potentially notable findings. First, 4 of the 6 patients experienced neurologic symptoms, including headache in patient 1, altered mental status in patient 2, and irritability and nuchal rigidity in patients 4 and 5. Only patient 4 underwent cerebral spinal fluid sampling, with findings consistent with aseptic meningitis, as has been described in Kawasaki disease. Further, patient 4 was found to have cerebral edema on head CT, a finding perhaps consistent with underlying central nervous system inflammation, though the pathogenesis of this finding is unclear. Second, all 6 of our patients had hyponatremia at presentation, as has been reported in Kawasaki disease and is perhaps associated with more severe inflammation and Kawasaki shock syndrome [9].

The patients in our cohort received therapies that have been used successfully for the treatment of Kawasaki disease, including IVIG and methylprednisolone. In most patients, this was highly effective in reducing systemic inflammation, as evidenced by resolution of fever, with improving cardiac function over a period of days. Overall, 5 of the 6 patients described in this cohort have been discharged from the hospital.

In summary, we report our recent experience in caring for 6 patients with evidence of prior SARS-CoV-2 infection with a hyperinflammatory syndrome consistent with MIS-C. Additional epidemiologic and clinical data are needed to measure prevalence of this condition, evaluate its association with SARS-CoV-2, and determine if it is a distinct clinical syndrome or a forme fruste of Kawasaki disease.

#### Note

*Financial support.* This work was supported by the Agency for Healthcare Research and Quality (K12HS026393-01 to K.C.).

**Potential conflicts of interest.** All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

#### References

- 1. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet **2020**; 395:1607–8.
- New York City Health Department. 2020 Health Alert #13: Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19. Available at: https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/ covid-19-pediatric-multi-system-inflammatory-syndrome.pdf. Accessed 7 May 2020.
- Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed 18 May 2020.
- Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020; 145: e20200702.
- Coronavirus disease 2019 in children—United States, February 12-April 2, 2020. Morbid Mortal Wkly Rep 2020; 69:422–426.
- Jones TC, Muhlemann B, Veith T, et al. An analysis of SARS-CoV-2 viral load by patient age. Available at: https://virologie-ccm.charite.de/fileadmin/user\_upload/ microsites/m\_cc05/virologie-ccm/dateien\_upload/Weitere\_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age-v2.pdf. Accessed 7 May 2020.
- 7. Yun SH, Yang NR, Park SA. Associated symptoms of Kawasaki disease. Korean Circ J **2011**; 41:394–8.
- Baker AL, Lu M, Minich LL, et al.; Pediatric Heart Network Investigators. Associated symptoms in the ten days before diagnosis of Kawasaki disease. J Pediatr 2009; 154:592–595.e2.
- Schuster JE, Palac HL, Innocentini N, et al. Hyponatremia is a feature of Kawasaki disease shock syndrome: a case-control study. J Pediatric Infect Dis Soc 2017; 6:386–8.