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

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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, on 14 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 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 z score, 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,
Table 1. Clinical Features of 6 Children With Multisystem Inflammatory Syndrome in Children

| 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 – – +a – + –
- Fissured lips/strawberry tongue – + +a + – –
- Lymphadenopathy – – – – – –
- Extremity edema – + – – + –
- 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)
- Lymphocyte count (cells/μL) 170 510 300 910 1200 970 (Ref: 970–3960/μL)b
- 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: 0.0–4.3 ng/mL)

Cardiopulmonary support

- Ventilation support MV NI NI MV None MV
- Vasoactive support Epi, NorEpi Epi, Mil – Epi, Mil Epi, Dopa Epi, NorEpi, Dobut, Mil

Antifibrotic therapies

- Number of doses of intravenous immunoglobulin (2 g/kg) 1 1 1 2 2 1
- Methylprednisolone 2 mg/kg/day + – + + + +
- Other antifibrotic therapy – +a – +a – + a

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 Positivea Positivea Negative Positivea
- Tracheal aspirate SARS-CoV-2 PCR Negative ND ND Negative ND ND
- Anti-SARS-CoV-2 immunoglobulin G Positiveb 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; Dopa, dopamine; Dox, doxycycline; Epi, epinephrine; F, female; M, male; Met, metronidazole; Mil, milrinone; MV, mechanical ventilation; 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.

aDeveloped this feature on hospital day 5.
bThere 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.

Methylprednisolone 10 mg/kg once (prior to admission to our institution).

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

Acute kidney injury defined as an increase in serum creatinine ≥1.5 times the upper limit of normal.

SARS-CoV-2 PCR testing positive with a high cycle threshold.

Obtained after intravenous immunoglobulin.
### Table 2: Laboratory Features of Six Children With Multisystem Inflammatory Syndrome in Children

| Laboratory Feature                        | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6* |
|-------------------------------------------|-----------|-----------|-----------|-----------|-----------|------------|
| White blood cell count ($\times 10^3$/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 $\times 10^3$/μL²            |           |           |           |           |           |            |
| Absolute lymphocyte count (cells/μL)      |           |           |           |           |           |            |
| Initial                                   | 170       | 510       | 300       | 910       | 1200      | 970        |
| Minimum                                   | 170       | 510       | 300       | 250       | 300       | 320        |
| Ref 970–3960 cells/μL^(a)                 |           |           |           |           |           |            |
| Hemoglobin (g/dL)                         | 12.5      | 11.2      | 12.4      | 11.2      | 11.0      | 9.6        |
| Initial                                   | 7.2       | 7.8       | 9.2       | 6.9       | 9.2       | 7.4        |
| Minimum                                   | 64        | 175       | 117       | 92        | 33        | 175        |
| Ref 11.5–15.5 g/dL^(b)                    |           |           |           |           |           |            |
| Platelets ($\times 10^9$/μL)              | 150       | 175       | 180       | 98        | 48        | 217        |
| Initial                                   | 64        | 175       | 117       | 92        | 33        | 175        |
| Ref 150–400 $\times 10^9$/μL              |           |           |           |           |           |            |
| Creatinine (mg/dL)                        | 2.5       | 0.9       | 0.7       | 0.5       | 1.6       | 3.6        |
| Initial                                   | 125       | 154       | 132       | 129       | 131       | 128        |
| Maximum                                   | 75        | 53        | 38        | 29        | 98        | 108        |
| Ref: 136–145 mg/dL^2                      |           |           |           |           |           |            |
| Alanine aminotransferase (IU/L)           | 3.6       | 2.6       | 4.3       | 4.0       | 2.6       | 2.4        |
| Initial                                   | 6.73      | 1.01      | 27.76     | 6.66      |           |            |
| Minimum                                   | 3.30      | 11.51     | 2.15      | 27.76     | 16.24     |            |
| Ref: 3.7–5.8 IU/L^2                      |           |           |           |           |           |            |
| C-reactive protein (mg/dL)                | 34.3      | 28.8      | 14.7      | 16.8      | 30.7      | 8.3        |
| Initial                                   | 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 mg/dL                       |           |           |           |           |           |            |
| Procalcitonin (ng/mL)                     | 3.6       | 2.6       | 4.3       | 4.0       | 2.6       | 2.4        |
| Initial                                   | 6.73      | 1.01      | 27.76     | 6.66      |           |            |
| Minimum                                   | 3.30      | 11.51     | 2.15      | 27.76     | 16.24     |            |
| Ref: 3.7–5.8 g/dL^3                      |           |           |           |           |           |            |
| Albumin (g/dL)                            | 37.6      | 27.2      | 44.1      | 29.5      | 32.1      | 24.8       |
| Initial                                   | 4.3       | 2.6       | 4.3       | 4.0       | 2.6       | 2.4        |
| Minimum                                   | 3.30      | 11.51     | 2.15      | 27.76     | 16.24     |            |
| Ref: 0.0–0.489 μg/mL                     |           |           |           |           |           |            |
| Ferritin (ng/mL)                          | 1096.2    | 1267.0    | ND        | 512.6     | 804.2     | 768.0      |
| Initial                                   | 1096.2    | 1267.0    | ND        | 748.1     | 804.2     | 1162.0     |
| Ref: 13.7–78.8 ng/mL                     |           |           |           |           |           |            |
| International normalized ratio            | 1.11      | 1.34      | 1.62      | 1.27      | 1.05      | 1.23       |
| Initial                                   | 1.66      | 1.34      | 1.69      | 1.56      | 1.05      | 2.50       |
| Maximum                                   | 1.66      | 1.34      | 1.69      | 1.56      | 1.05      | 2.50       |
| Ref: N/A                                  |           |           |           |           |           |            |
| Lactic dehydrogenase (U/L) – initial only | 903       | ND        | ND        | 1059      | 728       | 885        |
| Ref 420–750 U/L^3                         |           |           |           |           |           |            |
abdominal pain, diarrhea, mucus 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 HD 2 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 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 crisis. One of the most unique features of this disease is its rela-
sulting pandemic of COVID-19 is an ongoing global health

**DISCUSSION**

The recent emergence of SARS-CoV-2 in humans and the re-
sulting data collection of COVID-19 is an ongoing global health
crisis. One of the most unique features of this disease is its rela-

**Note**

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