A 2-Year-Old Girl with Multisystem Inflammatory Syndrome in Children (MIS-C)

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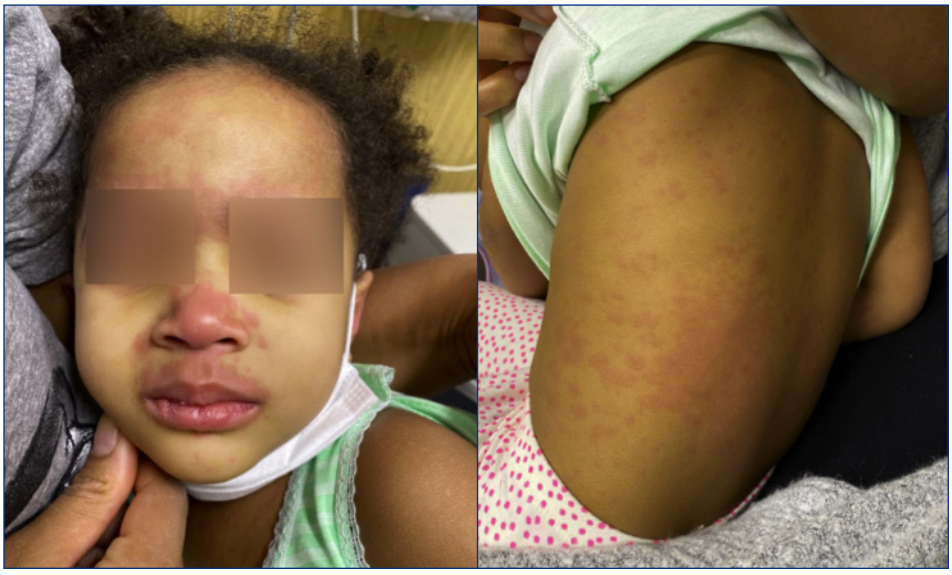
From the Case Records of the Alpert Medical School of Brown University Residency in Emergency Medicine

DR. REBECCA LEVIN: A 2-year-old otherwise healthy female presented to the pediatric emergency department (ED) with fever, fussiness and worsening rash. Her first visit to the pediatric ED was on day of illness number two where she was noted to have a fever to 101°F, rhinorrhea, mild abdominal pain but an otherwise normal exam. COVID-19 PCR testing was performed and she was discharged home with antipyretic instructions. The following day she developed an itchy, raised, red rash on her left foot that progressed cephalad and ultimately involved her legs, back, trunk, arms and face. The rash spared her palms and soles and coalesced periorally. The patient was evaluated by her pediatrician who diagnosed her with hand-foot-and-mouth disease and sent her home with supportive care.

The child returned to the ED on day of illness number five with concern for persistent fevers, worsening rash and irritability. Her COVID test sent from the first ED visit was negative. Her exam was notable for irritability and discomfort, erythematous posterior pharynx without exudate, tachypnea (respiratory rate in the 30s) with clear breath sounds, and tachycardia (heart rate 140s) with otherwise normal heart sounds. Her abdomen was soft but diffusely tender without rigidity or guarding. She had no lymphadenopathy. She had a diffuse erythematous macular rash over her entire body sparing the palms and soles. It was now coalesced around the mouth and nose but also involved the forehead/brow region as well as her upper and lower eyelids. The rash was pruritic and blanching without open lesions or vesicles (**Figure 1**).

Figure 1



DR. LYDIA CIARALLO: What is on your differential?

DR. LEVIN: The differential for fever and rash is, of course, very broad, and includes other viral illnesses, sepsis, Kawasaki disease, drug reaction, serum sickness, rickettsial infection, myocarditis, and oncologic processes. Other immunologic or rheumatologic syndromes such as systemic juvenile arthritis, hemophagocytic lymphohystiocytosis, and macrophage activation syndrome could be considered as well.

DR. ERIKA CONSTANTINE: Did she have any exposure to COVID-19?

DR. LEVIN: Both parents tested positive for COVID six weeks prior. Mom reported that both the patient and her siblings (14-year-old brother and 8-year-old sister) tested negative and have been asymptomatic. There was no other known exposure since that time. The patient does not go to daycare and her siblings are in online-only school. The mother works at a store and the father is a driver for a supply company.

DR. JONATHAN VALENTE: Does she meet the criteria for Kawasaki disease?

DR. ELIZABETH JACOBS: One must certainly entertain the diagnosis of Kawasaki disease in this patient. She had 5 days of fever with two additional clinical criteria:

erythematous pharynx and rash. However, she would require a total of four of the five clinical criteria of complete Kawasaki disease: conjunctival injection, oral mucous membrane involvement, peripheral extremity involvement, rash, and cervical lymphadenopathy.

DR. VALENTE: When should you also consider MIS-C?

DR. JACOBS: On May 14, 2020, the Centers for Disease Control and Prevention (CDC) issued the following case definition of MIS-C:

- "An individual aged <21 years presenting with fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptom."[1]

As there is a fair amount of overlap between the clinical presentations of MIS-C and Kawasaki disease (KD), labs and history of a known exposure to COVID-19 might help distinguish the two disease processes.

The age, race, and gender of the patient may also be helpful. The median age of children presenting with MIS-C is 9 years, while in the US the peak incidence of KD is in the 18–24 month age group[2,3] 66% of reported cases have occurred in Hispanic/Latino or Black/Non-Hispanic children while KD presents more commonly in Asian populations.[2,3]

While an elevated ESR and CRP are frequently both seen in either MIS-C or KD, thrombocytopenia, hyponatremia, and AKI are more characteristic of MIS-C. Shock can occur with either disease process but is more common with MIS-C than Kawasaki disease.

Our patient was found to have thrombocytopenia (platelets 86 x10^9/L) and hyponatremia (sodium 131 meq/L). While in the emergency department, she developed hypotension and shock requiring fluid resuscitation and cardiovascular support in the form of an epinephrine infusion. This constellation of lab findings, clinical presentation, and history of COVID-exposure made MIS-C the more likely diagnosis.

DR. JANE PREOTLE: When should MIS-C work-up be initiated and what does it entail? Should any specialists be consulted if there is concern for MIS-C?

DR. LEVIN: The definition of MIS-C is vague, and many febrile pediatric patients (especially early in their illness presentation) have not yet developed secondary symptoms of a viral illness (such as cough, rhinorrhea, or GI symptoms). Clinical suspicion and history/physical exam should focus on:

- Tachycardia (with or especially without fever)
- Persistent/refractory fever
- Altered mental status
- Hypotension
- Decreased urine output

For patients who are not critically ill, latest guidance recommends a tiered approach to the workup.[4] A flowchart published by the American College of Rheumatology outlining work-up for MIS-C can be found in **Figure 2**.[4] Of note, this flowchart only describes the work-up for MIS-C itself. All children undergoing MIS-C work-up should also be evaluated for other infectious and non-infectious causes of their symptoms.[1] This additional testing may include a group A strep testing, viral panels (either respiratory or stool), urinalysis, chest X-ray and blood cultures.

If patients are severely ill or hypotensive, it is important to include bacterial causes of sepsis in the differential, obtain cultures and initiate coverage with broad spectrum antibiotics.

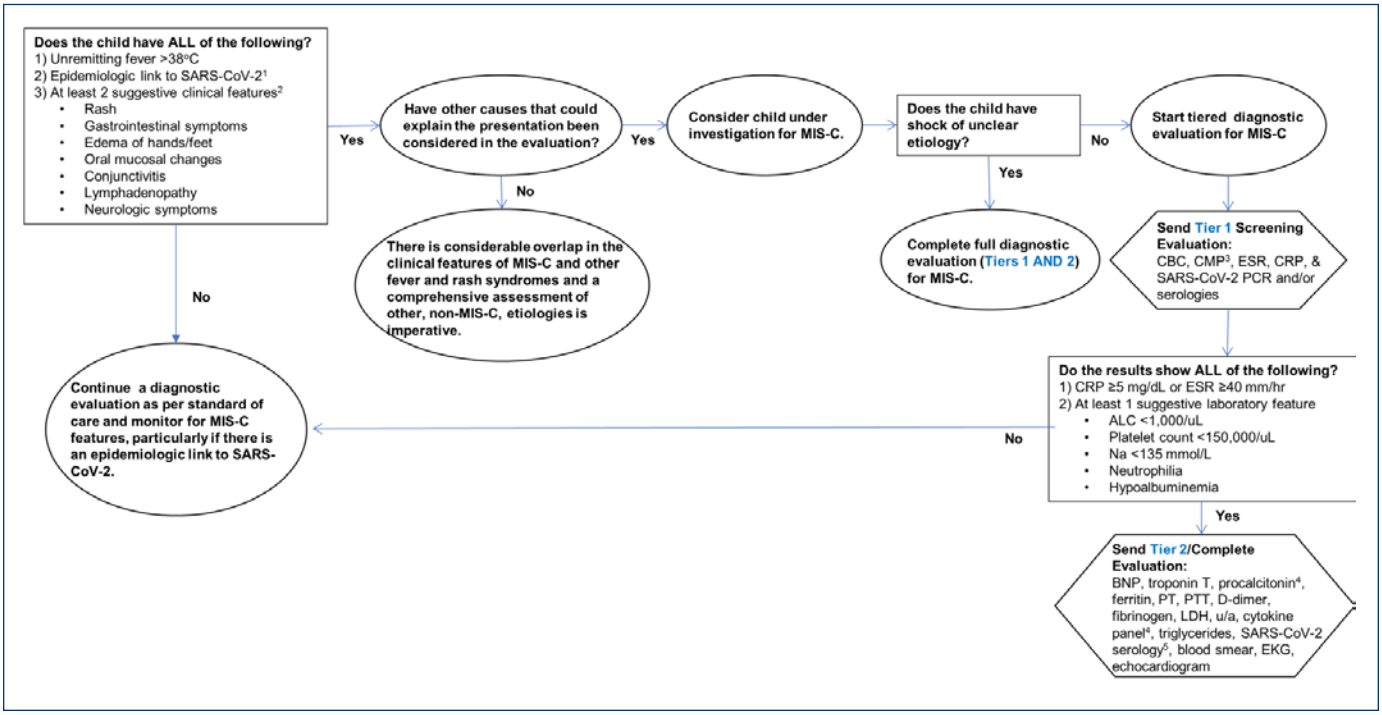
Because our understanding of this new disease process continues to evolve, the American Academy of Pediatrics Interim MIS-C guideline advises that patients with suspected MIS-C are best managed by a multidisciplinary pediatric team.[1] These teams differ by institution and may include (though are not limited to) pediatric infectious disease, rheumatology, cardiology, hematology, hospital medicine, and critical care specialists. This allows for careful deliberation of the diagnosis and potential need for specific treatments based off of each individual patient's clinical presentation.

DR. WILLIAM BINDER: What are the complications of MIS-C?

DR. JACOBS: MIS-C patients have been noted to have cardiac dysfunction, myocarditis, shock, and/or coronary artery aneurysms (CAA).[4,5] Thromboses have also been reported. Rarely, patients have required ECMO or died from these complications. In a New England Journal of Medicine report detailing children in New York State with MIS-C, 53% had myocarditis, and 8% had CAA's. 62% required vasopressor support.[6]

Certain demographic factors seem to be associated with an increased complication rate. In a recent retrospective study of over 1,000 patients who met the case definition of MIS-C, ICU admission was significantly more likely in older (age six years and above) children. The odds of developing shock also increased in the older age groups, with 2.5 times greater odds of developing shock in ages 13 and older as compared to children aged zero to five. Rates of complications such as decreased cardiac function, shock, and myocarditis were

Figure 2. Flowchart of suggested MIS-C work-up published by the American College of Rheumatology.[4]



similarly found for non-Hispanic Black patients as compared to non-Hispanic White patients. Coronary artery abnormalities were found more commonly in male patients.[7]

Our patient developed hypotension and shock requiring a continuous epinephrine infusion. Her coronary arteries were normal. She had an elevated troponin to 0.092 ng/mL and BNP >5000pg/mL. Her echocardiogram revealed mild four-chamber dilation, moderate biventricular systolic dysfunction, and mild bilateral AV valve regurgitation consistent with myocarditis. Of note, she also had a D Dimer that peaked at 2,064 ng/mL and she underwent bilateral upper and lower extremity ultrasound studies that were negative for thrombosis. Her SARS-CoV-2 antibody titers were positive.

DR. MELANIE LIPPMAN: What is the treatment of MIS-C? What is the prognosis of MIS-C?

DR. LEVIN: Patients should receive a screening echocardiogram for cardiac function and coronary artery anomalies. In addition to supportive care and blood pressure support as needed, treatments for MIS-C may include intravenous immune globulin (IVIG), steroids, anticoagulation, and/or aspirin. Medication regimens vary depending on several clinical factors and should be decided by a multidisciplinary team. Our patient received IVIG, steroids, and aspirin in addition to a continuous epinephrine infusion for hypotension.

Luckily, MIS-C is a rare complication of COVID-19 infection and children are recovering quite well, albeit frequently with need for intensive care level support. As of March 1, 2021, there were 2,617 cases of MIS-C meeting the case definition reported in the United States with 33 deaths attributed to complications from MIS-C (1.3%). There have been fewer than 24 cases in Rhode Island and fewer than 100 in Massachusetts.[2]

The patient was weaned off of the epinephrine infusion and her echocardiogram normalized prior to discharge. She was discharged home five days after admission on aspirin 81 mg daily in addition to a steroid taper. As of her last outpatient cardiology visits, she is doing well, her cardiac dysfunction has completely resolved, and she will continue to be followed closely.

DR. ERICA LASH: What else wouldn't you want to miss?

DR. LEVIN: Children undergoing work-up for possible MIS-C should also be evaluated for other infectious and non-infectious pathology. Several articles have discussed the potential harm of premature closure and anchoring on a diagnosis of MIS-C.[8-11] While we must have a low threshold to add MIS-C to our differential for pediatric patients, MIS-C remains relatively uncommon despite high numbers of COVID-19 cases in our communities. Many MIS-C patients may initially have clinical presentations that are consistent with more common, mild diagnoses such as viral illness or gastroenteritis that do not typically warrant lab workup or hospital admission. It is important for all providers to give families anticipatory guidance regarding reasons to return

to care such as continued fevers, mental status changes or ill appearance. The current diagnostic criteria for MIS-C are relatively nonspecific and rely upon clinicians to rule out any other potential diagnoses. There are many "do-not-miss" diagnoses that should be entertained. Among others, sepsis, bacteremia, myocarditis, appendicitis, tick-borne illnesses, and oncologic processes can have similar presentations. Like many MIS-C patients, our patient appropriately received empiric antibiotic coverage with ceftriaxone before a multidisciplinary team determined the patient's ultimate diagnosis.

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