
Posted May 28, 2020

ABSTRACT
Since late April 2020, data regarding Kawasaki-like syndrome and hyperinflammatory response in children associated with COVID-19 has rapidly emerged. Much remains unknown about the risk factors, pathogenesis, prognosis, and specific therapy for this emerging manifestation of COVID-19 known as Multisystem Inflammatory Syndrome in Children (MIS-C). MIS-C is rare and early recognition is crucial though no standardized treatment guideline have been established. Worldwide collaboration will be important as more cases are recognized going forward.

INTRODUCTION
In late April 2020, the United Kingdom’s National Health Service issued an alert about a new COVID-19 (SARS-CoV-2) manifestation in children. A cluster of previously healthy children became ill with overlapping symptoms of Kawasaki disease and toxic shock syndrome with lab parameters showing severe systemic inflammation. Since then, more cases were reported, mostly, from other European countries and the United States. As of May 14, 2020, New York State reported over a hundred cases of children who were hospitalized with this phenomenon, and sadly, 3 died. Prior to this, COVID-19 was thought to rarely cause harm to children, with most being asymptomatic or experiencing only mild respiratory symptoms. A better understanding of the impact of COVID-19 on children, especially when it causes critical illness, is needed.
WHAT IS CURRENTLY KNOWN ABOUT COVID-19 ASSOCIATED KAWASAKI-DISEASE-LIKE SYNDROME AND OTHER MANIFESTATIONS

It is unclear if COVID-19 causes KD or is a syndrome that mimics KD. The majority of data was generated from Europe and the US in an online meeting held in early May 2020. A group from the UK recently published a series of 8 children with this multisystem inflammatory syndrome and shortly after, another series of 10 children from Italy was also reported.1,5

In the UK series, 8 previously healthy children presented with vasoplegic shock and myocardial dysfunction, 5 male and 6 of Afro-Caribbean descent. All of them had unrelenting fever along with some features seen in KD (rash, conjunctivitis, peripheral edema). Interestingly, all had prominent gastrointestinal symptoms including non-bloody diarrhea, abdominal pain, and vomiting and imaging revealed ascites and ileitis. One child developed giant coronary aneurysm and another child died from refractory shock and a large cerebrovascular infarction.4

An observational study from the Bergamo province in Italy, which had a high rate of SARS-CoV-2 infections at that time, reported a 30-fold increased monthly incidence of KD in a cohort of children from February 18, 2020 to April 20, 2020, compared with a cohort of patients from the previous 5 years. Of 10 children, 7 were male, 5 presented with classic KD, 5 were classified as incomplete KD, and 5 patients met the criteria for Kawasaki shock disease syndrome and MAS.5

Laboratory findings in both cohorts demonstrated neutrophilia, lymphopenia, thrombocytopenia, marked elevation of inflammatory markers. Additionally elevated ferritin, elevated triglyceride and D-dimer were seen suggesting MAS/HLH. Most of the patients had significantly elevated proBNP (B-type natriuretic peptide) or troponin-T or both suggesting compromised cardiac function or shock state or both.

According to available data, the emerging phenotypes are a combination of typical/atypical Kawasaki disease, Kawasaki shock syndrome, toxic shock syndrome, and MAS/HLH. Common presentations are fever, rash, and gastrointestinal symptoms including abdominal pain, diarrhea, and vomiting. Unlike the adult presentation on COVID-19, most children have no significant respiratory involvement. Features of KD mucocutaneous inflammation (eg, conjunctivitis, rash, cervical lymphadenopathy) and systemic inflammation with single or multiple-organ involvement (eg, liver, renal, neurological) can be seen. A subset of patients developed coronary artery aneurysm as seen in Kawasaki disease. Severe cases presented with shock as a result of cardiac dysfunction with or without myocarditis in the setting of a hyperinflammatory state and required inotropic treatment with features resembling Kawasaki shock and toxic shock syndrome.
This phenomenon appears to result from an uninhibited immune response to a prior COVID-19 infection rather than a direct injury resulting from the acute viral infection. This is speculated from the observation that the surge of cases presented around 2 to 3 weeks after the peak of infection in the area and the majority of these children had a negative COVID-19 polymerase chain reaction nasopharyngeal swab test but positive viral serology. They were previously fit and well, without preceding COVID-19 symptoms, but some were with history of a COVID-19 sick contact.

The predilection for male gender is similar in classic KD and the KD-like syndrome associated with COVID-19; however, the syndrome associated with COVID-19 appears to affect older children (5 to 14 years) rather than younger children. These patients also have lower white blood cell count, lymphocyte and platelet counts, higher ferritin level, and elevated cardiac markers. In general, the incidence of classic KD is higher in children of Asian descent; however, it is interesting to point out that greater than 50% of the reported UK cohort with KD-like syndrome are of Afro-Caribbean descent. This observation may suggest a genetic susceptibility in this subgroup or reflect a higher rate of COVID-19 infection in this population.

The provisional name for this KD-like syndrome by experts in the UK is “Pediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PMIS-TS).” On May 14, 2020, the Centers for Disease Control and Prevention announced an official name calling this condition “Multisystem Inflammatory Syndrome in Children (MIS-C)” (Table 1).

**MANAGEMENT OF MIS-C ASSOCIATED WITH COVID-19 INFECTION**

As this is a new evolving spectrum of our understanding of COVID-19 infections in the pediatric population, there is much to learn. It is important to reiterate that MIS-C remains rare and has only occurred in a small number of children. Early recognition is crucial as these patients may be critically ill and require care in a pediatric intensive care unit as well as evaluation from multiple subspecialties including infectious disease, cardiology, hematology/oncology, and rheumatology.

At present, there is no standardized treatment guideline established for MIS-C. Direction of treatment depends on where patients fit into the spectrum of disease, and is largely based on experiences of the treating clinicians. Based on previous cases reported, patients meeting KD or atypical KD criteria or those with coronary artery changes should receive IVIG 2 g/kg. High dose aspirin has also been used in conjunction with IVIG. If hyperinflammatory features are prominent, immunosuppression is considered including the use of corticosteroids or biologic medications such as anakinra (anti-IL-1) or tocilizumab (anti-IL-6). Upregulation of the IL-1 signaling pathway is a highlighted mechanism in both MAS and KD, supporting the use of anakinra.

**REFERENCES**


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**TABLE 1**

Case definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

An individual < 21 years presenting with

- Fever, 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 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

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*Fever > 38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours.

*Including, but not limited to, 1 or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactate dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin.

RT-PCR = reverse transcription polymerase chain reaction

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