

Sirada Panupattanapong, MD

Center for Pediatric Rheumatology and Immunology,
Cleveland Clinic Children's

Elizabeth B. Brooks, MD, PhD

Center for Pediatric Rheumatology and Immunology,
Cleveland Clinic Children's

New spectrum of COVID-19 manifestations in children: Kawasaki-like syndrome and hyperinflammatory response

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.

The statements and opinions expressed in COVID-19 Curbside Consults are based on experience and the available literature as of the date posted. While we try to regularly update this content, any offered recommendations cannot be substituted for the clinical judgment of clinicians caring for individual patients.

doi:10.3949/ccjm.87a.ccc039

WHAT IS TRUE KAWASAKI DISEASE?

Kawasaki disease (KD) was first characterized in the 1960s. It is named after Dr. Tomisaku Kawasaki who described a series of Japanese children suffering from "acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes."¹ KD now occurs worldwide with a higher incidence in Eastern nations compared with Western nations.

KD is an acute, self-limited febrile illness that predominately affects young children, especially those less than 5 years with a median age of onset of 9 to 11 months. Approximately 25% of cases occur in older children and it rarely affects adults. It is more common in males than females by a ratio of 1.5 to 1.²

Despite over 50 years of intensive study, the exact etiology of KD remains unknown. The current concept is that this syndrome is a result of an immunologic response to an exposure in the respiratory system or gastrointestinal tract or both in genetically susceptible children. The immunologic cascade leads to systemic inflammation in medium sized arteries and multiple organs during the acute phase. As the incidence of KD peaks during the winter and spring, this has pointed towards infectious agents as a primary trigger.

The symptoms of KD (those not associated with COVID-19) can resemble acute infections such as viral infection, bacterial lymphadenitis, or scarlet fever. The diagnostic criteria for KD include:

- Fever for at least 5 days and
- The presence of at least 4 of 5 principle clinical features:
 - Extremity changes with erythema and edema of palms and soles during the acute phase. Skin peeling can be seen in the convalescent phase.

- o Diffuse polymorphic rash including maculopapular, diffuse erythroderma or erythema multiforme-like.
- o Bilateral non-exudative bulbar conjunctivitis typically sparing the limbus.
- o Oral mucosal changes with cracked lips, oral and pharyngeal erythema, “strawberry tongue” (erythema of tongue with prominent fungiform papillae).
- o Cervical lymphadenopathy, typically unilateral, 1.5 cm or greater in diameter.³

Some patients, particularly infants or older children, may present in an atypical manner and not fulfill the complete KD diagnostic criteria, thus known as incomplete KD. They may have spontaneous defervescence before 5 days or prolonged unexplained fever along with only 2 or 3 principle clinical findings. In this scenario, KD diagnosis can be made if 3 or more compatible laboratory findings exist (anemia, thrombocytosis, hypoalbuminemia, elevated alanine aminotransferase, leukocytosis, or leucouria) or if the presence of coronary artery dilatation or aneurysm on echocardiogram is noted.³

KD is the most common cause of acquired heart disease of children in the US and developed countries. Children with KD should receive treatment as 20% of untreated children can develop coronary artery aneurysm posing a significant risk of thrombosis and myocardial infarction in later life. Large size aneurysms may rupture and cause death. Severe cases of KD may present with shock state (Kawasaki shock disease syndrome) similar to what has been described currently in association with COVID-19. Rarely, macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) can complicate the course.

For classic KD, intravenous immunoglobulin (IVIG) is the cornerstone of therapy along with other adjunct treatments for patients with disease not responsive to IVIG including corticosteroids, cyclosporine, and biologics (anti-tumor necrosis factor and anti-interleukin [IL]-1). The primary purpose of treatment is to halt the acute systemic inflammatory process to prevent the development of coronary artery changes. Aspirin is given for antithrombotic effect.

■ 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.^{4,5}

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.⁵ 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.⁴ 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).”⁶ 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).⁷

■ 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

TABLE 1

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

An individual < 21 years presenting with

- Fever,^a laboratory evidence of inflammation,^b 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

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

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

RT-PCR = reverse transcription polymerase chain reaction

Reproduced from Centers for Disease Control and Prevention website.⁷

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.^{4,5} 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 in this setting.^{8,9} Anticoagulation may need to be considered if markedly elevated D-dimer occurs given the hypercoagulability and clot formation seen in adults with COVID-19.^{10,11} Cardiogenic shock and myocardial compromise can lead to fatal outcomes. Vigilant cardiac monitoring, serial cardiac markers (pro-BNP, troponin) and echocardiogram (focusing on cardiac function and coronary arteries) are also crucial.

■ REFERENCES

1. Kawasaki T. *Arerugi*. 1967;16(3):178–222.
2. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997–2007. *Pediatr Infect Dis J* 2010; 29(6):483–488. doi:10.1097/INF.0b013e3181cf8705

-
3. **McCrindle BW, Rowley AH, Newburger JW, et al.** Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association [published correction appears in *Circulation* 2019 Jul 30; 140(5):e181–e184]. *Circulation* 2017; 135(17):e927–e999. doi:10.1161/CIR.0000000000000484
 4. **Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P.** Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; 395(10237):1607–1608. doi:10.1016/S0140-6736(20)31094-1
 5. **Verdoni L, Mazza A, Gervasoni A, et al.** An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study [published online ahead of print, 2020 May 13]. *Lancet* 2020; 10.1016/S0140-6736(20)31103-X. doi:10.1016/S0140-6736(20)31103-X
 6. **Royal College of Paediatrics and Child Health.** Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. May 1, 2020. Accessed May 27, 2020. <https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf>
 7. **Centers for Disease Control and Prevention.** Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). CDC Health Alert Network publication CDCHAN-00432. May 14, 2020. Accessed May 27, 2020. <https://emergency.cdc.gov/han/2020/han00432.asp>
 8. **Sönmez HE, Demir S, Bilginer Y, Özen S.** Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. *Clin Rheumatol* 2018; 37(12):3329–3335. doi:10.1007/s10067-018-4095-1
 9. **Tremoulet AH.** Adjunctive therapies in Kawasaki disease. *Int J Rheum Dis* 2018; 21(1):76–79. doi:10.1111/1756-185X.13208
 10. **Klok FA, Kruip MJHA, van der Meer NJM, et al.** Incidence of thrombotic complications in critically ill ICU patients with COVID-19 [published online ahead of print, 2020 Apr 10]. *Thromb Res* 2020; S0049-3848(20)30120-1. doi:10.1016/j.thromres.2020.04.013
 11. **Poissy J, Goutay J, Caplan M, et al.** Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence [published online ahead of print, 2020 Apr 24]. *Circulation* 2020; 10.1161/CIRCULATIONAHA.120.047430. doi:10.1161/CIRCULATIONAHA.120.047430