

CONTAGIOUS COMMENTS

Department of Epidemiology

Update on Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)

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1. What is multisystem-inflammatory syndrome in children (MIS-C) and what do we know about the epidemiology?

- Multisystem inflammatory syndrome in children (MIS-C) is an emerging syndrome that was first recognized by pediatric providers in Europe in the spring of 2020. Since that time, cases have been described on six continents.
- This syndrome appears to be a post-infectious complication of SARS-CoV-2 infection that involves the immune response to the infection, but the immunologic mechanism behind the disease and what predisposes certain patients to MIS-C is not yet known.
- There is likely a broad range of illness severity in patients with MIS-C, but most of the current literature is focused on patients who require hospitalization.
- For severe cases of MIS-C that require hospitalization, patients present with signs and symptoms of profound systemic inflammation and can progress to severe illness in certain pediatric patients with evidence of injury or dysfunction of multiple organ systems.
- In the literature and our experience at Children's Hospital Colorado, approximately two-thirds of pediatric patients admitted to the hospital with MIS-C will require admission to the intensive care unit for treatment of hypotension and cardiac dysfunction.

2. What do we know about the epidemiology of MIS-C?

- Cases of MIS-C are temporally associated with SARS-CoV-2 infections, and the peak of MIS-C cases tends to occur approximately four to six weeks after the peak of SARS-CoV-2 and COVID-19 cases in these areas.
- Initial studies estimate the incidence to be 2 cases per 10,000 people less than 21 years of age, but this data was collected before the surge in cases seen in the United States in the late fall and winter.
- Patients who develop MIS-C may have had an asymptomatic or mild infection with SARS-CoV-2, and some families may not be aware that their child had an infection.
 - The median interval between infection and development of MIS-C symptoms is about 3 weeks.
- MIS-C affects children of all ages, but in the cases that have been described, the median age has been between 8 and 10 years of age.

3. What are the clinical symptoms associated with this newly described syndrome?

- Patients who have been diagnosed with MIS-C commonly present with the following symptoms:
 - Fever $>38.5^{\circ}\text{C}$ (typically for multiple days)
 - **Acute gastrointestinal symptoms** (vomiting, diarrhea, and prominent abdominal pain in up to 88% of patients)
 - Rash
 - Swollen hands and feet
 - Bilateral non-purulent conjunctivitis
 - Strawberry tongue
 - Hypotension or shock
- Patients have also presented with the following signs after work-up:
 - **Evidence of systemic inflammation**
 - **Cardiac involvement including ventricular dysfunction**, myocarditis pericarditis with or without pericardial effusion, valvulitis, or coronary artery dilation/aneurysms
 - Acute kidney injury
 - Liver involvement
 - Evidence of coagulopathy
- To meet criteria for MIS-C, patients should have evidence of a recent SARS-CoV-2 infection (see below) or have close contact with an individual with a confirmed or highly suspected SARS-CoV-2 infection (COVID-19 disease).
- In order to meet criteria for this disease, the patient cannot have another likely microbial cause including bacterial infection (bacterial sepsis, staphylococcal or streptococcal toxic shock syndrome) or viral infection that can be associated with cardiac involvement (enterovirus, influenza).
- It is important to remember that not every patient will meet all of the criteria, but most patients will meet at least some criteria.
- Diagnostic criteria have been established by multiple organizations including the Centers for Disease Control and the World Health Organization.

4. What laboratory findings are associated with MIS-C? (those in bold and italics appear to be more specific for MIS-C):

- High inflammatory markers (CRP, ESR, procalcitonin)
 - **CRP** can be very high (20-40 mg/dL)
- Elevated white blood cell count with high absolute neutrophil count and **low lymphocyte count**
- Anemia
- **Thrombocytopenia**
- Elevation in creatinine 1.5-1.9 times baseline OR increase >0.3 mg/dL
- Hypoalbuminemia
- Hyponatremia
- Elevated **D-dimer**, abnormal fibrinogen
- Elevated cardiac markers: troponin I, **NT-pro BNP**
- Elevated ferritin
- Possible positive SARS-CoV-2 PCR or antibody test

5. What is the best way to look for evidence of SARS-CoV-2 association in these cases?

- Given that many of these patients will present around 4 weeks after exposure to SARS-CoV-2, serologic testing, looking for an antibody response to SARS-CoV-2 is likely to be the most useful test to associate MIS-C cases with COVID-19.
- SARS-CoV-2 PCR should be sent from respiratory specimens to rule out continued shedding and for infection control purposes, but is less commonly detected by the time patients present with MIS-C.
- Infection control practices should be informed by testing for SARS-CoV-2 viral RNA as a sign of possible transmissibility, and not by serology, which suggests an antibody response to an infection which may no longer be active.

6. How is MIS-C related to Kawasaki Disease (KD)?

- Patients who meet criteria for MIS-C can have clinical and laboratory features that overlap with other inflammatory conditions including Kawasaki disease. However, even though these two syndromes share some common features, they are thought to be two different conditions with differing etiologies.
- Signs and symptoms that can overlap with KD include rash, bilateral non-purulent conjunctivitis, mucous membrane involvement (red lips/red tongue) and evidence of coronary artery dilation and aneurysms.
- Some important key difference between MIS-C and KD include:
 - KD primarily happens in the toddler age group (80% of cases are in children < 5 years old) whereas most cases of MIS-C have occurred in older children 5-15 years old.
 - Children with MIS-C are much more likely to have severe gastrointestinal complaints, cardiac involvement such as ventricular dysfunction and myocarditis (in addition to coronary involvement seen in KD), hypotension, and be more coagulopathic compared to children with KD.
 - Children with MIS-C are more likely to have lymphopenia, thrombocytopenia, and hyponatremia compared to children with KD. Additionally, the inflammation seen in children with MIS-C is usually higher than in children with KD.

7. How is MIS-C treated?

- All patients who have been diagnosed with MIS-C should receive standard supportive care including fluid resuscitation and vasoactive agents (epinephrine, norepinephrine, etc.) as necessary.
- Many patients will initially receive empiric antibiotics for potential bacterial infection while undergoing evaluation for sepsis. If serious bacterial infection is ruled out, antibiotics may be de-escalated or discontinued.
- The optimal treatment for patients with MIS-C continues to be evaluated but has not been established. Most experts recommend use of IVIG as well as immunomodulatory medications to decrease inflammation (infliximab, corticosteroids, or anakinra).

- New data suggest that children with severe presentations may benefit from more aggressive therapy initially.
- Consultation with pediatric infectious disease, cardiology, and rheumatology specialists should be used to guide therapeutics in this newly emerging condition.

8. Who should be evaluated for MIS-C?

- We recommend that patients with fever ≥ 3 days **AND** two or more of the clinical findings seen with MIS-C, including severe gastrointestinal complaints and/or clinical findings that overlap with Kawasaki disease (rash, red eyes, red lips/tongue, swollen cervical lymph nodes, or swelling of the hands/feet), be evaluated by a medical provider with laboratory studies done. Providers should have a higher suspicion for MIS-C in children with a known preceding SARS-CoV-2 infection or exposure to someone with COVID-19 in the preceding 2-6 weeks.
- Patients who meet the above clinical criteria may warrant initial screening labs to evaluate for inflammation, lymphopenia, and thrombocytopenia.
- It is important for parents and providers be on the lookout for children with potential MIS-C and KD as both likely benefit from earlier recognition and treatment.
- For patients with suspected MIS-C, the [Clinical Pathway](https://www.childrenscolorado.org/health-professionals/clinical-resources/clinical-pathways/) developed and used at Children's Hospital Colorado is now available for use by providers outside of our network of care.
<https://www.childrenscolorado.org/health-professionals/clinical-resources/clinical-pathways/>

9. What have we learned from the literature and our experience at Children's Hospital Colorado in treatment of patients with MIS-C?

- Patients can have profound abdominal pain and may undergo evaluation for appendicitis. Those who have undergone imaging have demonstrated evidence of enteritis and colitis without obvious appendicitis.
- Although patients with both MIS-C and KD present with elevated inflammatory markers, the relative degree of inflammation is generally higher in MIS-C (CRP can be as high as 20-40 mg/dL).
- Patients who have been treated for MIS-C more frequently have the following lab findings: hyponatremia, absolute lymphopenia, elevated NT-proBNP, and elevated troponin.
- Patients may develop hypotension quickly with distributive shock and signs of systemic capillary leak and cardiac dysfunction putting them at risk for fluid overload and pulmonary edema. We recommend early discussion with critical care medicine for patients with evidence of compensated or uncompensated shock for recommendations regarding fluid resuscitation and initiation of vasoactive agents.
- Patients with evidence of cardiac involvement (hypotension, ventricular dysfunction, myocarditis pericarditis with or without pericardial effusion, valvulitis, or coronary artery dilation/aneurysms) may improve more quickly with administration of immunomodulatory therapy plus IVIG as initial therapy.

10. What is Children's Hospital Colorado doing to manage patients with suspected MIS-C?

- Our team at Children's Hospital Colorado is well prepared to recognize and treat patients with MIS-C.
- Our infectious diseases, rheumatology, cardiology, emergency care, hospitalist and intensive care teams are part of an international working group of pediatric experts who are caring for these patients.
- We have a multidisciplinary team that frequently evaluates the emerging literature and is reviewing our own experience with management of these patients to make changes to our [Clinical Pathway](#) in order to improve recognition and treatment of children with MIS-C.

<https://www.childrenscolorado.org/health-professionals/clinical-resources/clinical-pathways/>

Resources:

- CDC Case Definition: <https://emergency.cdc.gov/han/2020/han00432.asp>
- WHO Case Definition: <https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>
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