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Children's Hospital Colorado

CONTAGIOUS COMMENTS
Department of Epidemiology

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 where did it come from?

- Multisystem inflammatory syndrome in children (MIS-C) is an emerging syndrome that was first recognized by pediatric providers in Europe. Pediatric hospitals in Europe initially reported an increase in cases of children presenting with gastrointestinal symptoms (vomiting and abdominal pain), prolonged fever, and signs of systemic inflammation including rash, swelling of hands and feet, and/or mucosal involvement (red eyes, strawberry tongue).
- Some patients with this syndrome can progress to become severely ill with very high inflammatory markers, evidence of impairment or injury of one or more organ systems, and hemodynamic instability that requires admission to the intensive care unit and use of vasopressors.
- Cases of MIS-C have been geographically and temporally associated with SARS-CoV-2 infections, with most cases occurring in areas of high incidence of COVID-19 an average of four weeks after the peak of SARS-CoV-2 in these areas.
- The epidemiologic and clinical data suggest that what we are seeing in children with MIS-C is likely a post-infectious or inflammatory response to the virus, as opposed to a result of acute, ongoing damage from the virus itself.

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

- Patients who have been diagnosed with MIS-C have commonly presented with the following symptoms:
  - Fever >38.5ºC (typically for multiple days)
  - Acute gastrointestinal symptoms (vomiting and abdominal pain, occasionally diarrhea)
  - 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**
  - Acute kidney injury

  - Liver involvement
  - Cardiac involvement including myocarditis (with LV dysfunction), pericarditis, valvulitis, or coronary artery dilation/aneurysms
  - 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 above, but most patients will meet at least some criteria.

3. What laboratory findings are associated with MIS-C?

- High inflammatory markers (CRP, ESR, procalcitonin)
- 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, pro-NT BNP
- Elevated ferritin
- Possible positive SARS-CoV-2 PCR or antibody test

4. 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 can 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.

5. Who is at risk for MIS-C?

- MIS-C affects children of all ages, but in the cases that have been described, the median age has been between 8 and 11 years of age.
- The syndrome has been noted to primarily appear between 4 and 6 weeks following the peak of COVID-19 illness in a given geographic area. The peak of COVID-19 illness so far in the state of Colorado was in late April, but it is important to note that

there are ongoing cases, so it is possible we will continue to see new cases of MIS-C while there is ongoing transmission in the community.
- Children who have contact with individuals who have had documented COVID-19 or who have had a clinical illness that would be consistent with COVID-19 are likely to be at higher risk for developing this disease.

6. How is MIS-C related to Kawasaki Disease (KD) and Toxic Shock Syndrome?

- Patients who have met criteria for MIS-C have had clinical and laboratory features that overlap with other inflammatory conditions including Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome.
- Signs and symptoms that have been reported include rash, bilateral non-purulent conjunctivitis, mucous membrane involvement (red lips/red tongue) and evidence of coronary artery dilation and aneurysms resembling Kawasaki disease.
- 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.
    - Although patients with both MIS-C and KD present with elevated inflammatory markers, the relative degree of inflammation is generally higher in MIS-C.
- The exact pathophysiology of MIS-C is not well understood, and research is being undertaken to understand the mechanism of inflammation and disease in these patients.
- Other patients have developed shock that includes elements of toxic shock syndrome with multiorgan system involvement, including cardiac dysfunction and hypotension. Cultures from patients with MIS-C, however, have been negative for streptococcal and staphylococcal bacteria.

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 has not been established. However, most experts currently recommend that patients who meet criteria for MIS-C should be treated with IVIG similar to how patients are treated for KD. Immunomodulatory medications (including corticosteroids, infliximab and anakinra) can be considered for those who do not respond to IVIG. Consultation with infectious disease and rheumatologic 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.
- 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.

9. What is Children's Hospital Colorado doing to prepare for patients with 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, and have formed a multidisciplinary team jointly drafting local guidelines to assist in recognizing and treating these patients.

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
- Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr. 2020; doi: 10.1542/hpeds.2020-0123
- New York State Department of Health. Health Advisory: Pediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19 interim case definition in New York State.
- Paediatric Intensive Care Society Statement: "Increased number of reported cases of novel presentation of multi-system inflammatory disease." April 27, 2020
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic [published online ahead of print, 2020 May 7]. Lancet. 2020;S0140-6736(20)31094-1. doi:10.1016/S0140-6736(20)31094-1
- Royal College of Paediatrics and Child Health. "Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19"
- Verdoni, L., Mazza, A., Gervasoni, A., Martelli, L., Ruggeri, M., Ciuffreda, M., Bonanomi, E., D'Antiga, L., 2020. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. The Lancet.. doi:10.1016/s0140-6736(20)31103-x

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