MIS-C

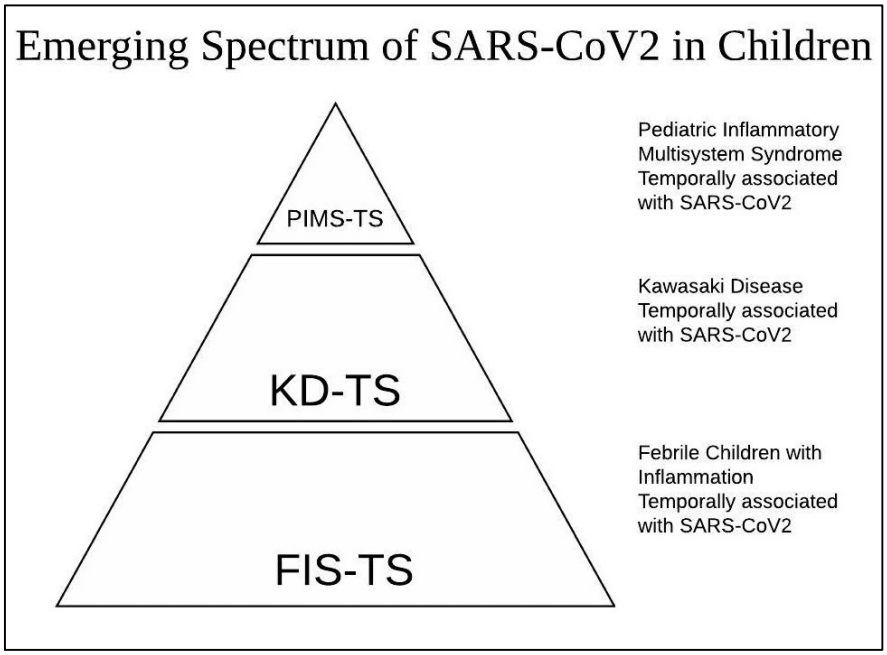
Multisystem Inflammatory Syndrome in Children

Overview

Areas hard hit by COVID-19 around the world have described a new pediatric illness that appears to follow a SARS-CoV-2 infection or exposure. Multisystem Inflammatory Syndrome in Children (MIS-C) is a clinical entity of uncertain etiology that involves significant hyper-inflammation, potentially leading to organ dysfunction and shock. Presentation features may overlap Kawasaki Disease or Toxic Shock Syndrome.

It is postulated that MIS-C is a post-infectious hyper-inflammatory process, rather than a manifestation of an acute infection. In case series in NYC and the UK, patients had antibodies for the virus despite negative nasopharyngeal SARS-CoV-2 PCR swabs.

As we gain experience with this new illness, it appears that MIS-C is on a spectrum of febrile, inflammatory illnesses associated with COVID-19. We do not know yet if they represent a single, continuous process or separate clinical entities with overlapping features, and it is unclear if that distinction is important in determining health outcomes in children with MIS-C.



Adapted from Michael Levin, "Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 –PIMS-TS," COCA Webinar, 19 May 2020

While we know that these patients are at high risk for developing cardiovascular collapse, resulting in the need for high levels of critical care support, what is less clear at this time is how these patients can be differentiated from those with more common pediatric febrile illnesses such as viral gastroenteritis or a urinary tract infection.

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This document and the associated algorithms are intended to help physicians understand the clinical presentation of MIS-C, providing a systematic framework for the evaluation and early diagnosis of patients with suspected MIS-C, when they are hopefully at lower risk of cardiovascular collapse. The algorithms are designed to be used **in addition** to your typical approach to the febrile pediatric patient.

Important Consideration

MIS-C is a very new syndrome, and little information exists in the literature regarding signs, symptoms, laboratory data, or best practices, such as basic care guidelines and treatment options. The medical community is still in the early stages of investigating this condition, and our understanding of MIS-C will surely evolve and change over time.

The recommendations found here are based on the expert opinions of pediatric specialists at C.S. Mott Children's Hospital. Our goal is to identify patients who are at risk for further clinical deterioration at a point prior to cardiovascular collapse, without including every child with a common febrile illness.

Keeping in mind our goal of differentiating patients with MIS-C from patients with more typical febrile childhood illnesses, we have recommended clinical criteria for initiating a laboratory workup, and then laboratory thresholds that warrant further observation and/or investigation. The clinician's judgment is an important factor as well and should be taken into consideration.

As MIS-C becomes better understood and more data become available, we anticipate that these guidelines will be updated periodically to reflect new information.

Presentation

Children with MIS-C exhibit signs and symptoms that significantly overlap with typical pediatric febrile illnesses. It is therefore important to consider the fever curve carefully. Patients universally present with prolonged or persistent fever and often complain of fever that is resistant to antipyretics. Most patients experience gastrointestinal symptoms, including abdominal pain, diarrhea, nausea, and vomiting. Additional features include rash, conjunctivitis, headache, and sore throat. A subset of patients present with shock and require high levels of supportive care in addition to coverage for sepsis and consideration for MIS-C.

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Concerning presenting signs and symptoms

- Persistent fever ≥ 38.5C
- Nausea, vomiting, diarrhea, abdominal pain (may mimic appendicitis)
- Rash
- Conjunctivitis
- Oral mucosal changes
- Headache, irritability
- Cough, shortness of breath
- Sore throat
- Chest pain
- Extremity swelling
- Lymphadenopathy

Initial Workup

As MIS-C is an inflammatory syndrome, the initial laboratory workup is focused on uncovering signs of inflammation. Moreover, as the disease progresses, patients often develop end-organ dysfunction, in particular cardiac involvement and coagulopathies, and the recommended testing seeks to screen for those concerns as well.
Note: Work-up of alternative diagnoses should be concurrent with initial MIS-C evaluation.

Initial laboratory testing

- CBCPD
- Comprehensive Panel
- CRP
- High Sensitivity Troponin
- Ferritin

Laboratory thresholds of concern:

- Absolute Lymphocyte Count < 0.5 k/uL
- Albumin <2 g/dL
- CRP > 10 mg/dL
- High Sensitivity Troponin >30 pg/mL
- Ferritin >350 ng/mL

Please refer to the Outpatient Algorithm for further decision-making guidance.

Case Definitions

Since MIS-C is such a poorly understood condition at this time, with more questions than answers, data collection is a high priority for the medical community and public health agencies around the world. The Centers for Disease Control and the World Health Organization have established case definitions and registries for the syndrome to allow for a more systematic approach to diagnosis, better recognition of risk factors and causality, and more standardized collection of data for subsequent research. At Michigan Medicine, we are using the CDC case definition.

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CDC case definition:

A. Age < 21 years
B. Clinical presentation including **all** of the following:
    1. Fever >38.0C (100.4F) for ≥ 24 hours or subjective fever lasting ≥24 hours
    2. Laboratory evidence of inflammation, including but not limited to:
        - Elevated CRP
        - Elevated ESR
        - Elevated fibrinogen
        - Elevated procalcitonin
        - Elevated D-dimer
        - Elevated ferritin
        - Elevated LDH
        - Elevated IL-6 level
        - Neutrophilia
        - Lymphcytopenia
        - Hypoalbuminemia
    3. Severe illness requiring hospitalization
    4. Multisystem (2 or more) involvement
        - Cardiovascular
        - Renal
        - Respiratory
        - Hematologic
        - Gastrointestinal
        - Dermatologic
        - Neurologic
C. No alternative plausible diagnosis
D. Recent or current SARS-CoV-2 infection or exposure, with **any** of the following:
    - Positive SARS-CoV-2 RT-PCR
    - Positive serology
    - Positive antigen test
    - 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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Multisystem Inflammatory Syndrome in Children
Outpatient Quick Reference

Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly recognized inflammatory syndrome presenting in pediatric patients, associated with current or recent SARS-CoV-2 infection. Much is still unknown, but we do know that children present with prolonged or persistent fever and a constellation of variable symptoms, along with many markers of significant inflammation. They are at high risk for cardiovascular collapse. This document accompanies the MIS-C protocol and is designed to be a quick reference guide when initiating evaluation of these patients in the outpatient setting.

Initial evaluation criteria
T ≥ 38.5C for at least 3 days, plus 2 or more concerning signs/symptoms
No other etiology identified

Concerning signs and symptoms
- Persistent fever ≥ 38.5C
- Nausea, vomiting, diarrhea, abdominal pain (may mimic appendicitis)
- Rash
- Conjunctivitis
- Oral mucosal changes
- Headache, irritability
- Cough, shortness of breath
- Sore throat
- Chest pain
- Extremity swelling
- Lymphadenopathy

Initial lab testing and thresholds of concern:
- Absolute Lymphocyte Count < 0.5 k/uL
- Albumin <2 g/dL
- CRP > 10 mg/dL
- High Sensitivity Troponin >30 pg/mL
- Ferritin >350 ng/mL

Note: Work-up of alternative diagnoses should be concurrent with initial MIS-C evaluation

To order labs:
If patient is being seen at a Michigan Medicine clinic:
- Place STAT order for Initial Labs in MiChart
- Labs are drawn per usual procedures for PUI in clinic

If patient does not have an appointment (eg, telehealth visit or at an outside office):
- Place STAT order for Initial Labs in MiChart, or have patient bring in lab requisition
- Direct patient to own clinic site or one of the lab/clinics below—there is no need to call first
  - When patients arrive, they will be screened at the door.
  - Family should inform the screener: "My child has a fever, and my pediatrician has ordered labs."
  - Clinic staff will take the patient to a respiratory isolation space with appropriate PPE

Brighton Health Center
8001 Challis Road
Brighton, MI 48116
810-227-9510
Mon-Thurs: 7am-7pm
Fri: 7am-5pm
Sat: 8am-12 noon

Canton Health Center
1051 N. Canton Center Road
Canton, MI 48187
734-844-5400
Mon-Thurs: 7:30am-7:30pm
Fri: 7:30am-5pm
Sat: 8am-12 noon

West Ann Arbor
380 Parkland Plaza
Ann Arbor, MI 48103
734-998-7370
Mon-Thurs: 7am-7pm
Fri: 7am-5pm
Sat: 8am-12 noon

C.S. MOTT CHILDREN'S HOSPITAL
MICHIGAN MEDICINE

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