Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance

What is the case definition of multisystem inflammatory syndrome in children (MIS-C)?

The CDC issued a Health Advisory on May 14, 2020, that outlines the following case definition for MIS-C:

- An individual aged <21 years presenting with fever,[1] laboratory evidence of inflammation,[2] 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 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

What are the common signs and symptoms of MIS-C?

Signs and symptoms include persistent fever, inflammation (based on laboratory test results), and evidence of clinically severe illness requiring hospitalization, with multisystem involvement.

Although different presentations have been described, common symptoms include:

- Kawasaki-disease-like features: conjunctivitis, red eyes; red or swollen hands and feet; rash; red cracked lips, swollen glands. In some children, coronary artery enlargement and/or aneurysms have been described. Some children presenting with Kawasaki disease-like syndrome have been noted to have a broader age range and presentation with more gastrointestinal (abdominal pain or diarrhea) and neurologic (headaches/meningitis) manifestations.
- Gastrointestinal symptoms such as abdominal pain, diarrhea, nausea/vomiting (patients have presented with colitis, hepatitis, and questionable appendicitis).
- Toxic shock syndrome-like features with hemodynamic instability and poor heart function.Cytokine storm/macrophage activation or hyperinflammatory features.
- Thrombosis or acute kidney injury.
- Shortness of breath suggestive of congestive heart failure or pulmonary embolism.
- Respiratory symptoms typically reported in adults with COVID-19 may not be present in pediatric patients with MIS-C.

Common laboratory findings in case reports have included:

- An abnormal level of inflammatory markers in the blood, including elevated ESR/CRP and ferritin, LDH.
- Lymphopenia <1000, thrombocytopenia <150,000, neutrophilia.
- Elevated B-type natriuretic peptide (BNP) or NT-proBNP (pro-BNP), hyponatremia, elevated D-dimers.

When should you suspect MIS-C as part of your differential diagnosis?

MIS-C is a rare complication temporally associated with COVID-19. Any child with suspected MIS-C should also be evaluated for infectious and noninfectious etiologies.

Persistent fever without a clear clinical source is the first clue. Any fever that is accompanied by symptoms concerning in their severity or coincident with recent exposure to a person with COVID-19 should raise suspicions.

Some children clinically progress rapidly and may develop hemodynamic compromise. These children should be followed and cared for in a hospital with tertiary pediatric/cardiac intensive care units whenever possible.

When should I perform testing for MIS-C and what sort of testing should I start with in the outpatient or emergency department setting?

Evaluate a child with persistent fever (≥3 days) who is moderately to severely ill with clinical signs of organ dysfunction (e.g. gastrointestinal, respiratory, cardiac, skin, or neurologic). Initial evaluation should include measurement of vital signs, assessment of perfusion and oxygen saturation. Early consultation and coordination with the nearest pediatric infectious disease and rheumatology specialist and pediatric referral center for optimal testing and management should be considered. Laboratory screening for systemic inflammation may be considered and initial lab screenings may include complete blood cell count (CBC) with differential, urine analysis, ESR, and CRP, with the addition of ferritin, LDH, comprehensive metabolic panel, pro-BNP, troponin, and fibrinogen depending on initial clinical suspicion and/or evidence of inflammation on initial lab screening. Note that none of these laboratory studies is specific for the diagnosis of MIS-C, so even if there is evidence of significant systemic inflammation, alternative diagnoses must still be considered (e.g., pyelonephritis, appendicitis).

Evaluation of severely ill appearing or hemodynamically fragile patients
Severely ill-appearing patients and those in compensated shock or shock should be evaluated and treated in the emergency department/critical care setting. Transfer to a referral center should be arranged. Laboratory tests, as described above, should be performed for initial evaluation regardless of duration of fever. Consultation with pediatric subspecialists (infectious diseases, cardiology, rheumatology) at a local or regional pediatric referral center should be initiated but should not delay transfer to a referral center.

What testing is needed for hospitalized children?

Any child sick enough to warrant admission for fever, abdominal pain, diarrhea, and/or organ dysfunction in whom MIS-C is suspected should be cared for in a hospital with tertiary pediatric/cardiac intensive care units. Although decisions about additional testing will be made by the multidisciplinary team managing the patient, pediatricians can prepare families for an expanded laboratory and cardiac workup that may include:

- Chest radiograph, EKG, and troponin. If any of these or physical examination is abnormal, then consult with pediatric cardiology and consider additional diagnostic testing for myocardial injury (echocardiogram and/or cardiac MRI).
- Expanded laboratory tests including pro-BNP, triglycerides, creatine kinase, amylase, blood and urine culture, D-dimer, prothrombin time/partial thromboplastin time (PT/PTT), INR, CRP, ferritin, LDH, comprehensive metabolic panel, and fibrinogen, if not already conducted.
- In all cases, COVID-19 testing should be performed with RT-PCR assay and serologic testing. Later serology may be needed if all negative initially. Serologic tests must be sent prior to administration of intravenous immunoglobulin (IVIG).

What is the recommended treatment approach for MIS-C?

Clinicians who suspect MIS-C in a child should use a multidisciplinary approach involving many pediatric specialists, which may include but is not limited to cardiology, infectious disease, immunology, hematology, rheumatology, pediatric hospital medicine, and critical care, to guide individual patient treatment. There are 3-4 sub-types of MIS-C that may require slightly different management based on evolution of symptoms and laboratory values. Optimal treatment for a patient with MIS-C is not known; however, is best determined by the multidisciplinary clinical team. The following interventions have been used:

- If patients appear hypotensive and septic during evaluation for MIS-C, treatment with antibiotics, fluid resuscitation, and if necessary, inotropes is appropriate until bacterial infection has been ruled out.
- Patients with MIS-C are usually treated with IVIG, 2 grams/kg (max of 100 grams); patient cardiac function and fluid status influence the duration of the infusion of IVIG therapy.
- Patients who do not improve clinically, or whose laboratory values do not improve, have also been treated with steroid therapy (ranging from 2 to 30 mg/kg/day of methylprednisolone depending on severity of illness) and biologics (eg. anakinra, 2 to 10 mg/kg/day, subcutaneously or intravenously, divided every 6 to 12 hours). A recent large observational study found that initial treatment with both IVIG and steroid therapy led to earlier resolution of fever compared to IVIG alone. Due to rapidly evolving treatment recommendations, consultation with pediatric subspecialists is strongly recommended.
- If the patient has laboratory or imaging evidence of myocardial injury or findings concerning for coronary artery aneurysms, discussion with pediatric cardiology is suggested prior to use of steroids.
- Patients treated with steroids and/or biologics often go home with a 3-week taper of steroids and/or biologics.
- All patients with MIS-C, unless there are contraindications (eg. platelets <100,000 or active bleeding), should be started on low-dose aspirin for thromboprophylaxis. Consultation with cardiology and hematology should take place to determine whether further intervention is required.

What infection prevention and control recommendations should be followed for MIS-C patients?

Patients who are hospitalized with suspected MIS-C should be considered patients under investigation for COVID-19. RT-PCR and antibody testing for COVID-19 (if available) should be performed. Local infection control policies should be followed.

Patients in whom MIS-C is diagnosed should be reported to the local or state public health department.

What is the recommended follow-up for MIS-C patients?

Patients diagnosed with MIS-C should have close outpatient pediatric cardiology follow-up starting 1 to 2 weeks after discharge. Timing should be determined in consultation with a pediatric cardiologist. Patients diagnosed with myocardial injury must have cardiology directed restriction and/or release for activities.

Patients who receive steroid therapy or treatment with biologics should receive follow-up with the pediatric rheumatologist following discharge.

Discharge of patients diagnosed with MIS-C should be coordinated with the patient's medical home. Primary care follow-up is recommended for all patients.

References

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[1]*Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours.*
[2]*Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.*

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