

**Multi-system Inflammatory Syndrome in Children (MIS-C) Temporally Associated with COVID-19**  
**Hasbro Children's Hospital Clinical Guideline**  
**Last updated February 2021**

This clinical guideline is a working, iterative document given the nature of this emerging clinical syndrome, with growing evidence and experience. The guideline will be updated as recommendations evolve.

**To meet the [CDC definition of MIS-C](#), you need ALL 5 of these things:**

1. An individual aged <21 years
2. Presenting with fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours)
3. Laboratory evidence of inflammation (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, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
4. No alternative plausible diagnoses
5. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms

AAP Interim Guidance: <https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/>

Additional resources:

<https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf>

<https://www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway>

### **RI DOH/CDC Reporting**

MIS-C is a reportable illness. The primary team caring for the patients at the time of discharge should complete the CDC form (<https://www.cdc.gov/mis-c/pdfs/hcp/mis-c-form-fillable.pdf>), and email to Diane Brady ([diane.brady@health.ri.gov](mailto:diane.brady@health.ri.gov)) at the Rhode Island Department of Health **with a patient facesheet** via a Lifespan secure protected health information (PHI) email or via secure fax at 401-222-2488. RIDOH will forward the information on to the CDC. The primary team should place a Significant Event note in the EMR noting that RIDOH/CDC reporting has been completed.

### **Description of patients**

- Likely pediatric/young adult patients (wide age range, with average age 8-11 years old)
- Signs and symptoms are consistent with post-infectious immune response/cytokine storm syndromes
- Often history of mild COVID-19 illness or exposure to close contact with COVID-19 within the past 4 weeks
- Pediatric patients with **acute** COVID-19 respiratory illness can also present with or evolve into a significant inflammatory state
- As above, similarities with many immune response syndromes such as Kawasaki Disease with shock, cytokine release syndrome, Hemophagocytic Lymphohistiocytosis (HLH), Macrophage Activation Syndrome (MAS)
- Differential including but not limited to the following should be considered:
  - Sepsis and septic shock
  - Kawasaki Disease with and without shock
  - Myocarditis

- Viral illness
- Rickettsial infection
- Toxic shock syndrome
- Staph scalded skin
- Serum sickness
- Acute presentation of new oncologic process
- Presenting with or can rapidly progress to shock, often cardiogenic
- Some male predominance, obesity prevalence, and disproportionately affecting Hispanic and Black populations

#### Presenting signs and symptoms

- Persistent fever, often refractory to anti-pyretics
- Diarrhea, abdominal pain, vomiting
- Rash (can be desquamating, not vesicular)
- Neurologic symptoms/altered mental status
- Tachycardia
- Hypotension
- Poor perfusion
- Hypoxia

#### Common laboratory findings

- Elevated D-dimer
- Elevated ferritin
- Elevated CRP/ESR
- Elevated troponin
- Elevated BNP
- Lymphopenia, sometimes with neutrophilia
- Thrombocytopenia
- Hyponatremia
- SARS-CoV-2 PCR can be negative or positive; often but not always SARS-CoV-2 IgG/IgM antibody positive

#### Signs and symptoms to consider referral/transfer to Emergency Department

Clinical suspicion and history consistent with syndrome, with special attention to:

- Tachycardia (with or especially without fever)
- Persistent/refractory fever
- Altered mental status
- Hypotension
- Decreased urine output
- Hypoxia

#### Suggested initial hospital workup/evaluation

Initial screening for patients with clinical exam and history suspicious for MIS-C:

- CBC with differential
- CRP
- ESR
- CMP/M/P

If patient presents initially with signs of shock or the initial lab findings are consistent with possible MIS-C (CRP  $\geq$  3 mg/dL and/or ESR  $\geq$  40 mm/hr, AND lymphopenia  $<$  1k or thrombocytopenia  $<$  150k or Na  $<$  135 or abnormal creatinine for age), consider obtaining the following additional workup:

- Ferritin
- Fibrinogen
- D-dimer
- PT/INR
- PTT
- Troponin
- BNP
- RPP2 (includes rapid SARS-CoV-2 PCR)
- SARS-CoV-2 antibody panel
- Blood culture
- Blood gas with lactate
- Urinalysis
- CXR
- 12 lead EKG
- For patients with evidence of shock/end organ dysfunction, consider echocardiogram in consultation with Pediatric Cardiology

On admission, additional evaluation may include:

- Triglycerides
- CK-MB
- LDH
- Type and screen

And consultations to the following services should be initiated:

- Cardiology
- Infectious Disease
- Rheumatology
- Hematology/Oncology
- Surgery if ECMO is being considered

#### Clinical decision-making regarding admission status

- Patients with suspicion for MIS-C should be admitted
- Patients who are hemodynamically stable may be admitted to wards with cardiorespiratory monitoring and frequent clinical re-assessment; otherwise patients should be admitted to the PICU
- Patients with persistent tachycardia, any worsening perfusion, or other metrics of declining cardiac output or increasing oxygen demand should be evaluated by the FAST Team with low threshold for immediate transfer to PICU
- All patients under consideration for MIS-C should have consultation by a multi-disciplinary team as described above

#### Therapies and interventions

- If hypotensive, consider appropriate early inotropic support prior to third fluid bolus, or earlier in patients who appear adequately hydrated
- Echocardiogram can guide fluid resuscitation management by identifying possible myocardial dysfunction and assessing preload

- Consider fluid management carefully as respiratory failure in patients has tended to occur after significant fluid resuscitation
- Early consideration of the need for central access
- Empiric antibiotics for sepsis
- Initiate thromboprophylaxis as per Pediatric COVID-19/MIS-C Thromboprophylaxis guideline and in consultation with Pediatric Hematology/Oncology (updated as of December 2020)

For patients with **mild disease** (no evidence of cardiac involvement):

- Initiate steroids (oral prednisolone, oral prednisone, or IV methylprednisolone 1 mg/kg BID, maximum 30 mg BID) in conversation with consultants
- Often will continue steroids for 5 days and then taper
- For patients meeting Kawasaki Disease criteria, treat per established guidelines in conjunction with steroids, as described above, for patients with epidemiological link to COVID-19 (close contact, antibody or PCR +)

For patients with **moderate to severe disease** (evidence of cardiac involvement, which may include or develop into shock/end organ dysfunction):

- For patients with moderate to severe presentations: in addition to steroids, initiate IVIG in conversation with consultants (2 g/kg/dose based on ideal body weight)
- Consider running large volumes of IVIG over longer periods of time to prevent fluid overload
- Consider diuretic dose after IVIG if hemodynamically stable
- Consider anakinra in conversation with consultants for patients refractory to IVIG
- Anti-viral therapy usually not indicated; discuss with consultant services
- Discuss ECMO early for refractory cardiogenic shock

#### Diagnostic monitoring

- Serial echocardiograms as clinically indicated
- Trend CBC, CRP, troponin, BNP, ferritin, fibrinogen, PT/INR, PTT, D-dimer, CMP as clinically indicated and in conjunction with consultant guidance

#### Discharge criteria

- Patients should meet all normal discharge criteria, as well as stable cardiac function and no fever (without anti-pyretics) for 24 hours

#### Contributors

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